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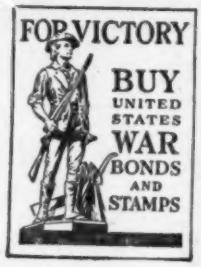

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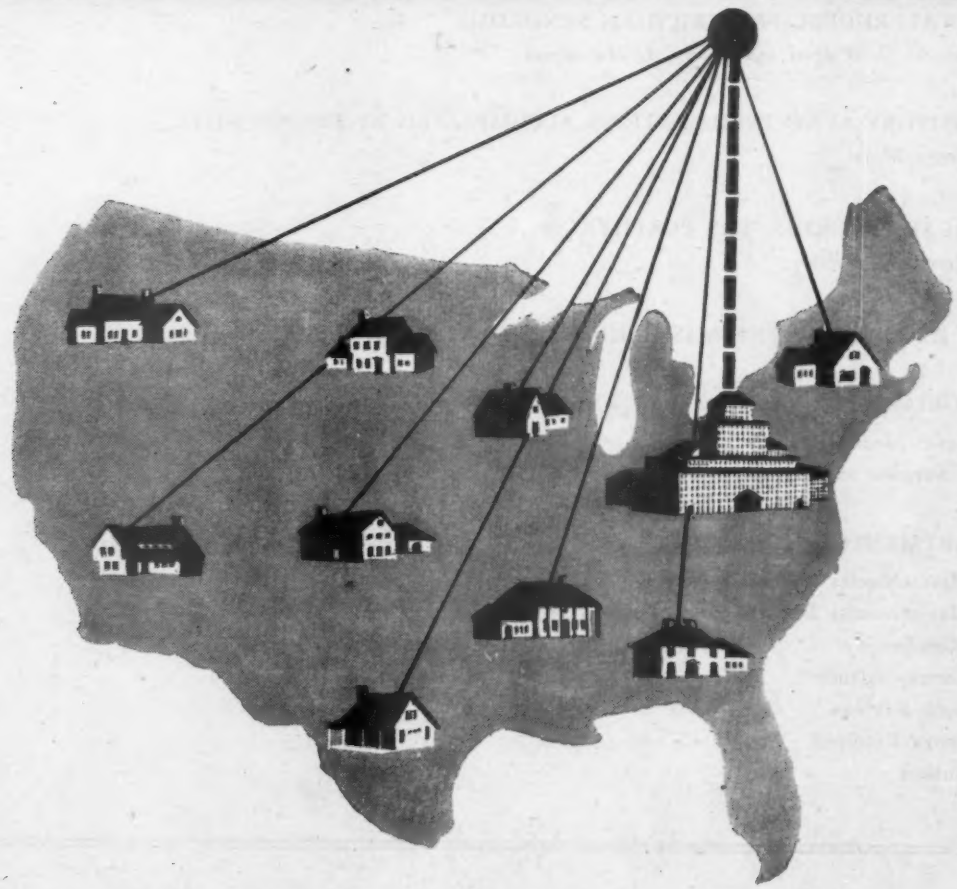

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THE WATERHOUSE–FRIDERICHSEN SYNDROME

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THE Waterhouse–Friderichsen syndrome is a clinical entity first described in 1911 by Waterhouse[1] in an eight-month-old child. In 1918, Friderichsen[2] reviewed the literature and described a similar case with a fulminating course, characterized clinically by stupor, cyanosis, pallor, vomiting and a rapidly spreading purpuric eruption, and at autopsy by massive bilateral adrenal hemorrhages. This syndrome is associated with a bacteremia, the etiologic agent in the majority of cases being the meningococcus. Although the pneumococcus, hemolytic streptococcus and staphylococcus have also been inculpated, considerable doubt has been cast on the role of any of these organisms as the offending agent.

Most of the cases have occurred in children, but with the recent and widespread increase in meningococcal infections there have been many additional reports of this syndrome in adults.[3–5] Although in the majority of reported cases the patients succumbed within twenty-four hours of onset, a few survived for as long as forty-eight hours. Recently, 2 cases with survival periods of eighty and eighty-eight hours both proved by autopsy, were described.[6] Evidently this syndrome is not universally fatal, for there are 6 cases of recovery on record.[7–12]

We have observed 6 cases of the Waterhouse–Friderichsen syndrome — 5 with a fatal outcome and 1 with recovery — in a large series of meningococcal infections encountered at a station hospital. This presentation is an attempt to correlate the clinical, pathological and laboratory data obtained in these cases. The literature on recovery from this syndrome will be reviewed, and an additional case will be presented in detail.

CLINICAL FEATURES

The clinical manifestations of the Waterhouse–Friderichsen syndrome have not been generally recognized. The paucity of clinical investigations is probably due to several factors, namely, failure in diagnosis, a fulminating course and the scarcity of cases seen by any one observer. The increasing prevalence of meningococcal infections has focused the attention of clinicians on this syndrome, and it is reasonable to suppose that it will be recognized more frequently in the future. The clinical features of our 5 fatal cases have been so similar as to warrant detailed discussion. The case with recovery varied slightly from the others and will be described separately.

The prodromal symptoms were similar to those encountered in any respiratory infection, consisting of headache, chilly sensations, muscular pains and malaise. The onset of the bacteremia was sudden and dramatic. The most striking features were the profound shock and the petechial eruption, which in the course of a few hours became purpuric. The skin lesions varied in size from small petechiae several millimeters in diameter to large, violaceous purpuric areas widely distributed over the body. They did not disappear on digital pressure, and in some cases necrosis and sloughing followed in the later stages. The patients were apprehensive and restless. Despite an initial temporary delirium, mental lucidity was maintained throughout. There was pallor of the face and trunk. In addition, a nephritic type of facial edema was present. The lips and extremities were cold and cyanotic. Perspiration was profuse. Vomiting, persistent diarrhea and abdominal pain were frequent complaints.

The temperature was moderately elevated early in the disease, ranging from 100 to 102°F., but within twenty-four to thirty-six hours it dropped to normal and remained at normal or slightly subnormal levels until death. The pulse rate was accelerated throughout. The respirations were rapid and shallow during the initial shock, but with recovery from it they became slower and deeper. Twenty-four hours before death they rose sharply, averaging 48 per minute. Of particular interest is the fact that respirations ceased a few minutes prior to the failure of heart function.

Early in the disease, hypotensive blood-pressure levels were encountered. Frequently diastolic readings were unobtainable. With recovery from the initial shock the blood pressure rose to quasi-normal levels.

Soon after the onset, a few scattered moist rales were audible at both lung bases. This condition

gradually progressed until numerous coarse, bubbling rales could be heard over both lung fields. With the appearance of frank pulmonary edema terminally, the patient lapsed into coma and died shortly thereafter.

Remarkably little attention has heretofore been paid to the initial anuria, which was a constant finding in these cases. The anuria persisted for twenty-four to thirty-six hours and was replaced by a severe oliguria. At no time was adequate renal function re-established, despite recovery from shock, evidenced by normal blood-pressure readings, the improved character of the pulse and the improved clinical appearance of the patient.

TABLE 1. *Laboratory Features.*

Case No.	Culture		Blood Pressure	Urine	White-Cell Count	Blood Chemical Findings*					Outcome
	Blood	Spinal Fluid				Chloride	Nonprotein Nitrogen	Creatinin	Icteric Index	Sodium	Potassium	
			mm. Hg.			*mg./100cc.*	*mg./100cc.*	*mg./100cc.*		*mg./100cc.*	*mg./100cc.*	
1	+	+	0/0	Anuria	33,000							Death (2 hr.)
2	+	−	90/60	Anuria								Death (13 hr.)
3	+	+	52/22 initially and 102/62 terminally	Anuria followed by oliguria; incontinence.	73,150	454 470	46 67	5.8 9.0	13.7	373 403	10.2 10.0	Death (40 hr.)
4	+	−	60/40 initially and 82/60 terminally	Anuria followed by oliguria; specific gravity 1.008 and 1.010; albumin +; microscopic examination negative.	47,250		86					Death (80 hr.)
5	+†	−	60/40 initially and 120/70 terminally	Anuria followed by oliguria; albumin ++; 50–60 red cells per high-power field, and hyaline and granular casts.	66,950	 412	52 91 96.9	 7.0 7.4				Death (88 hr.
6	+	+	68/0 initially	Anuria (41 hours) followed by return of renal function; specific gravity 1.010, 1.001 and 1.020; albumin +; microscopic examination negative.	49,350	396 412 479	 64 70 78 50	 5.4 4.7 3.6 3.2	6.0	 345 324 271	 16.9 19.8 12.8	Recovery

*Blood samples for clinical readings in Cases 3, 5 and 6 were taken on successive days after admission.
†Meningococcus found on routine peripheral blood smear.

Laboratory Data

No significant biochemical studies of the Waterhouse–Friderichsen syndrome have hitherto been reported. We have therefore devoted some attention to the study of electrolyte balance and renal function. The data in all 6 cases are summarized in Table 1.

The blood chemical changes were investigated in 4 cases. All the patients exhibited elevation of the nonprotein nitrogen level. In 3 cases, this finding was observed within twelve hours of onset and ranged between 52 and 64 mg. per 100 cc.; in 1 case, the blood was examined terminally. In all cases, the nonprotein nitrogen rose steadily, 96.9 mg. being the highest recorded level. Associated with this change was an early elevation of the blood creatinin, the concentrations varying between 5.4 and 9.0 mg. It is worthy of comment that the elevation of the nonprotein nitrogen was moderate, whereas that of the creatinin was marked. The icteric index showed a slight elevation to 13.7 in one of the fatal cases (Case 3). In contrast, the patient in Case 6, who recovered, had an icteric index of 6.0. In 3 cases (Cases 3, 5 and 6), the blood chloride levels were within normal limits.

In 2 patients (Cases 3 and 6), sodium and potassium determinations were done. Both showed slight sodium retention — 403 and 345 mg., respectively (normal, 315 to 340 mg.). In the case with a fatal outcome, the sodium continued to rise; in the recovered case, on the other hand, it dropped to a subnormal concentration. In the former the potassium was low, — 10 mg. (normal, 16 to 22 mg.), — where-

as in the latter it was normal. With recovery, however, the blood potassium also fell to a subnormal level.

A marked leukocytosis was observed in 5 cases, a blood-cell count being obtained in the other case. The white-cell count varied between 33,000 and 73,150, with a substantial increase in neutrophils. Although in some cases the initial counts were only moderately elevated, they invariably exhibited extreme leukocytosis during the subsequent twenty-four hours.

Urinalysis was done in all cases from which specimens could be obtained. Fixation of the specific gravity, and varying degrees of albuminuria, were noted. Interestingly enough, Case 4 demonstrated, in addition, a microscopic hematuria and cylindruria.

Neisseria intracellularis was cultured from the blood of each case. Despite grossly and microscopically negative spinal fluids, the cultures in 3 cases were positive.

Pathological Findings

Characteristic morphologic changes do exist in the Waterhouse-Friderichsen syndrome. Failure to recognize these structural variations may be attributed to the fact that such changes are progressive and become well defined only in those cases that have a prolonged clinical course. In reviewing the literature, we were impressed by the reports of the unusual brevity of this syndrome, the majority of patients succumbing within twenty-four hours, with an occasional survival period of forty-eight hours. In a previous publication we[6] reported 2 proved cases with prolonged survival periods and discussed the characteristic pathological features in detail. Since these observations have an obvious bearing on the subject of this paper, the previous studies have been extended to include the remaining cases of the syndrome. Post-mortem examinations were performed in all the fatal cases (Table 2). In evaluating these findings, it must be stressed that there is a vast difference in the morphologic structure of the liver, kidney and heart in short-lived cases as compared with that of those with longer survival periods.

The lungs revealed pleural effusion and pulmonary edema.

The adrenal glands were enlarged, varying in weight between 11 and 26 gm. Hemorrhagic areas were present bilaterally in the cortex and medulla. The shortest-lived cases (Cases 1, 2 and 3) showed the most extensive interstitial hemorrhages. It is evident from these observations that the length of survival is determined by the severity of destruction of adrenal tissues.

The livers were enlarged, weighing between 1950 and 2790 gm., except for that in Case 1, which weighed 1690 gm. The largest livers were seen in Cases 4 and 5, which had the longest survival periods. The microscopic changes varied in direct proportion to the survival time. In the shortest-lived cases (Cases 1 and 2), the sole finding was a mild hepatitis of the central zone. In Case 3, in which the patient survived for forty hours, an early necrosis of the central zone was present. In Case 4, with a survival time of eighty hours, there was dissociation of the liver cords of the central zone, with severe necrobiosis of the hepatic cells, midzonal necrobiosis and vacuolization of the hepatic cells, and a normal peripheral zone. However, Case 5, with a survival

Table 2. *Pathologic Features.*

Case No.	Lungs	Heart*	Ascitic Fluid cc.	Liver	Kidneys	Adrenal Glands
1	Pleural effusion (500 cc.); pulmonary edema.	Weight 300 gm.; cloudy swelling of muscle fibers.	None	Weight 1690 gm.; mild hepatitis of central zone.	Weight, 160 gm. left and 160 gm. right; normal histologically.	Weight, 16 gm.; severe bilateral hemorrhages.
2	Pleural effusion (scant); pulmonary edema.	Weight 370 gm.; cloudy swelling of muscle fibers.	None	Weight 1960 gm.; mild hepatitis of central zone.	Weight, 140 gm. left and 135 gm. right; normal histologically.	Weight, 11 gm.; severe bilateral hemorrhages.
3	Pleural effusion (250 cc. right, and 100 cc. left); pulmonary edema.	Weight 350 gm.; pericardial effusion (100 cc.); cloudy swelling and fragmentation of muscle fibers and interstitial edema.	None	Weight 1950 gm.; early necrosis of central zone.	Weight, 145 gm. left and 160 gm. right; increased cellularity and avascularity of glomerular tufts, cloudy swelling of convoluted tubular epithelium, and albuminous casts.	Weight 26 gm.; moderate bilateral hemorrhages.
4	Pleural effusion (200 cc. right and 200 cc. left); pulmonary edema.	Weight 410 gm.; pericardial effusion (50 cc.); same as Case 3 but severer.	1000	Weight 2035 gm.; dissociation of liver cords in central zone and severe necrobiosis of hepatic cells in central zone and midzone.	Weight, 170 gm. left and 185 gm. right; histologically same as Case 3 but severer.	Weight, 15 gm.; moderate bilateral hemorrhages.
5	Pleural effusion (500 cc. right and 75 cc. left); pulmonary edema.	Weight 590 gm.; pericardial effusion (75 cc.); same as Case 3 but severer.	500	Weight 2790 gm.; dissociation of liver cords, severe necrobiosis in central zone and midzone and early necrosis of hepatic cells in peripheral zone.	Weight, 280 gm. left and 240 gm. right; histologically same as Case 3 but severer.	Weight, 20 gm.; moderate bilateral hemorrhages.

*All cases except Case 1 revealed dilatation of the right auricle and ventricle.

period of eighty-eight hours, revealed similar although severer central and midzonal changes than did Case 4 and, in addition, early necrobiosis of the cells in the peripheral zone.

The kidneys were enlarged in only 2 cases (Cases 4 and 5), in which together they weighed 355 and 520 gm., respectively. The histologic architecture in Cases 1 and 2 was normal. In Cases 3, 4 and 5, with clinical courses of forty, eighty and eighty-eight hours, respectively, the microscopic features, although similar to one another, again were severest in the cases with the longest survivals. These consisted of increased cellularity and avascularity of the glomerular tufts, cloudy swelling of the proximal convoluted tubular epithelium and albuminous deposits in the tubular lumens. It therefore seems justifiable to conclude that significant renal changes are found only in those cases with prolonged survival periods.

The heart was grossly abnormal in 4 of the 5 fatal cases (Cases 2, 3, 4 and 5). These abnormalities consisted of cardiac hypertrophy, with the weight varying between 350 and 590 gm., and with marked dilatation of the right auricle and right ventricle. Pericardial effusion occurred in Cases 3, 4 and 5. No noteworthy gross changes were present in Case 1, in which the patient survived for two hours. The myocardium in all 5 cases revealed microscopic findings of a nonspecific character and were similar to those found in other infectious diseases and septicemias. Cloudy swelling was observed in all cases, but in addition, Cases 3, 4 and 5 disclosed fragmentation of the muscle fibers and interstitial edema. These degenerative changes were most advanced in the cases with the longest clinical courses.

The lungs, liver, spleen, kidneys and brain exhibited severe congestion. Petechiae were distributed over the serous membranes, gastrointestinal tract and heart — subendocardium, epicardium and papillary muscles. Pleural, pericardial and peritoneal serous effusions were found that clotted spontaneously. In only 1 case (Case 3) was a purulent inflammation of the meninges present.

Diagnosis

It is appropriate at this point to consider the diagnostic problem posed by the Waterhouse–Friderichsen syndrome. Since the incidence of this entity is constantly rising, the necessity for uniform criteria can hardly be disputed. From a survey of the foregoing material, there have been gathered clinical and laboratory data on which a diagnosis of this syndrome can be based. The following points are regarded to be of diagnostic significance: petechial eruption rapidly becoming purpuric; severe shock; facial edema; anuria of twenty-four to thirty-six hours' duration, followed by marked oliguria; urinalysis showing fixation of the specific gravity, albuminuria, hematuria or cylindruria; marked leukocytosis; isolation of the meningococcus by culture and, in some cases, by peripheral blood smear; renal failure, as evidenced by elevation of the blood nonprotein nitrogen and creatinin; and elevation of the blood sodium and diminution of the blood potassium.

A diagnosis of this syndrome cannot be based solely on any isolated factor mentioned above. On the basis of these studies it is concluded that the clinical signs per se are sufficient to warrant the diagnosis in acute, fulminating cases. With a more prolonged course, however, additional factors involving the alterations in blood chemistry, as well as the isolation of the meningococcus, must be consistently present to confirm the diagnosis.

Treatment

The therapeutic approach in the Waterhouse–Friderichsen syndrome resolves itself into the treatment of shock, toxemia and bacteremia and the administration of adrenocortical hormone substitution therapy.

Shock is combated in the usual manner. The employment of heat and stimulants and the anti-shock position are advocated. Parenteral fluids in quantities of 3000 to 4000 cc. should be given cautiously over a twenty-four-hour period. The intravenous administration of 500 cc. of plasma, repeated in twelve hours, is recommended because of its osmotic effect, mirrored in a noticeable elevation of the blood pressure. The use of epinephrin, in our experience, is of questionable value.

Toxemia is the gravest problem encountered in this entity, and the pathologic changes are directly attributable to it. Although at the present time there is no clear evidence that serotherapy is of value in meningococcal infections, it seems advisable to administer antimeningococcus serum in adequate amounts — 60,000 to 120,000 units — intravenously within the first twenty-four hours.

The control of meningococcemia has been made possible by the advent of chemotherapy. Of all the sulfonamide drugs, sulfadiazine is the derivative of choice. The necessity for massive doses of this drug, parenterally and orally, is apparent when one considers the overwhelming character of the bacteremia. The initial dose of sulfadiazine in this series was 5 gm. intravenously and 8 gm. orally. This was followed by large oral doses until a total of 25 to 30 gm. had been given within the first twenty-four hours. The blood-sulfadiazine concentration was used as a guide for determining the size and frequency of subsequent doses. The optimal blood level was considered to be 15 to 20 mg. per 100 cc.

The rationale of adrenocortical hormone substitution therapy in the Waterhouse–Friderichsen syndrome has been directed toward combating adrenal dysfunction resulting from the extensive hemorrhages and necrosis. The hope that this form of organotherapy would succeed in tiding the patient

over his critical period has met with disappointment. Experience indicates that its value is questionable. No resultant clinical improvement could be detected in the 4 cases in which it was used. Nevertheless, it may have contributed to the prolongation of the clinical course.

Recovery

Only 6 cases of the Waterhouse–Friderichsen syndrome with recovery have been reported in the literature.[7–12] A review of these cases failed to reveal any uniform criteria for diagnosis. The meningococcus was the etiologic agent in 5 of these cases. The pneumococcus was isolated from the case reported by Bickel.[7]

The diagnosis of recovery in this entity must necessarily be based solely on the clinical findings and laboratory data, because no pathologic evidence is available. It must be emphasized that fulminating meningococcemia associated with shock may simulate the Waterhouse–Friderichsen syndrome, but in the former autopsy fails to disclose any adrenal hemorrhages. From our observations, it is concluded that the important clinical differentiation of these two types is that in meningococcemia with shock no anuria and oliguria or retention of nitrogenous products in the blood occurs, whereas they are consistently present in the Waterhouse–Friderichsen syndrome. The cases of Carey,[8] Peabody[10] and Rucks and Hobson[11] showed many features that are found in the above criteria for diagnosis, particularly the purpuric manifestations, shock, anuria and oliguria, leukocytosis and elevation of the blood nonprotein nitrogen level.

In a previous publication, we[6] maintained that recovery was unlikely because of the basic morphologic changes found at post-mortem examination in protracted cases. In retrospect, this statement should be modified, because a case with recovery has since been observed. It is believed that the bacteremia, toxemia and resulting adrenal hemorrhages are quantitative; that they may be lethal or sublethal can hardly be questioned. It is not inconceivable, therefore, that this triad with its train of pathologic changes may be mild to moderate and fully compatible with recovery.

The following case is presented in detail as an example of recovery from the Waterhouse–Friderichsen syndrome. Interestingly enough, the clinical course and laboratory findings were not unlike those in the case reported by Peabody.[10]

Case Report

An 18-year-old soldier was admitted to a station hospital complaining of headaches, nausea and pains in the neck and back. On admission the temperature was 102°F., the pulse 92, and the respirations 36. Physical examination was essentially negative except for coryza and a red, injected pharynx. Three hours later the patient became delirious and irrational. He vomited bile-stained fluid and passed frequent, involuntary watery stools. Petechiae were first observed at that time. The blood pressure was 60/0, and the pulse 130. A lumbar puncture revealed clear spinal fluid under normal pressure, which was negative on laboratory examination. A white-cell count taken shortly after admission was 17,050, with 80 per cent neutrophils. A diagnosis of meningococcemia was made and treatment with 8 gm. of sulfadiazine by Levin tube was instituted. Subsequent sulfadiazine therapy consisted of 3 gm. every 3 hours. Parenteral fluids and 1 cc. of metrazol were administered intravenously.

The patient lapsed into a stuporous state 8 hours after entry. The temperature remained at 102°F. Examination disclosed slight facial edema. Numerous violaceous, petechial and purpuric areas were widely distributed over the trunk and extremities. Nuchal rigidity was absent. No abnormal neurologic signs could be elicited. The blood pressure was 68/0. A second white-cell count was 49,350, with 83 per cent neutrophils. The blood-sulfadiazine level was 13.8 mg. per 100 cc., and the blood chlorides 396 mg. Urinalysis could not be done because of complete anuria since admission. Blood and spinal-fluid cultures were positive for *Neisseria intracellularis* (Type I). A diagnosis of severe meningococcemia complicated by adrenal hemorrhages (Waterhouse–Friderichsen syndrome) was made. Intensive sulfadiazine therapy was continued orally, and 5.5 gm. of sodium sulfadiazine dissolved in sterile distilled water was administered intravenously. In addition, 30,000 units of meningococcus antitoxin with 1 cc. of epinephrin and 5 cc. of adrenocortical hormone was given by intravenous drip and repeated 6 hours later.

On the 2nd hospital day, 28 hours following admission, the patient was clinically improved. He appeared rational and the blood pressure rose to 72/40. The temperature was 99.4°F., the pulse 70, and the respirations 18. Despite intensive administration of fluids, the anuria persisted. The urinary bladder could not be palpated. The patient continued to vomit and complained bitterly of diffuse abdominal pain and diarrhea.

He received 27 gm. of sulfadiazine during the first 24 hours of therapy. The white-cell count fell to 23,950, with 96 per cent neutrophils. Complete blood chemical studies were done and were reported as follows: nonprotein nitrogen, 64 mg.; creatinin, 5.4 mg.; sugar, 101 mg.; chloride, 412 mg.; sodium, 345 mg.; potassium, 16.9 mg.; and icterus index, 6.0. The blood pressure rose to 80/60.

Vigorous sulfonamide therapy was continued, and a dosage schedule of 3 gm., alternated with 2 gm., administered orally every 3 hours was initiated. A blood sulfadiazine level of 14.4 mg. per 100 cc. was reported at that time. Renal function was re-established 41 hours after admission, at which time the patient spontaneously voided 540 cc. of dark-amber urine, which had a specific gravity of 1.010 and showed a moderate trace of albumin and a few white cells.

On the 3rd day, facial edema and asthenia were still present. The temperature fluctuated between 100 and 102°F. The blood pressure continued to climb, reaching 100/78. Blood chemical determinations were repeated, with the following results: nonprotein nitrogen, 70 mg.; creatinin, 4.7 mg.; sodium, 324 mg.; and potassium, 19.8 mg. The blood sulfadiazine was maintained at a satisfactory concentration of 16.6 mg. The total fluid intake was 4120 cc., and the urinary output 1100 cc. The sulfadiazine was then reduced to 2-gm. doses, alternated with 1 gm., every 4 hours. Throughout the remainder of the first week, there was fixation of the urinary specific gravity at 1.010.

Definite improvement was observed on the 4th day. The asthenia was considerably lessened. The first laboratory findings to confirm the clinical impression of recovery were a fall in the creatinin level to 3.6 mg. and one in the sodium level to 271 mg., with a concomitant fall in the potassium level to 12.8 mg. The nonprotein nitrogen was reported as 78 mg., a slight rise over the previous level. The blood chloride continued to increase, having attained a level of 479 mg. The white-cell count was 24,750, with 96 per cent neutrophils. The blood-sulfadiazine level was 19.5 mg., representing a slight increase over the previous reading. The fluid intake and urinary output were 3840 cc. and 2640 cc., respectively.

On the 6th day, the facial edema had completely disappeared, the purpuric lesions had faded and the temperature returned to normal for the first time. The white-cell count was 14,000, with 80 per cent neutrophils. The nonprotein nitrogen dropped to a level of 50 mg., and the creatinin to 3.2 mg. The sulfadiazine was discontinued.

The clinical course from that time on was one of progressive improvement. The sole complicating feature was a

temporary exhaustion and delirium state that occurred on the 17th day, characterized by depression, auditory and visual hallucinations and a recurrence of the asthenia that lasted for 6 days. The patient made a complete recovery and was discharged to his unit 46 days after hospitalization. Subsequent examinations showed no sequelae, and the patient was able to resume full military duties.

The clinical course in this case was similar to that in the 5 fatal cases, but differed from it in that renal function was restored and an elevated temperature was maintained. The re-establishment of renal function heralded recovery and was the most important prognostic sign. The rise in the nonprotein nitrogen and the creatinin occurred early in the course of the illness.

Discussion

Although cognizant of differences of opinion, we are inclined to agree with Martland[4] and Herbut and Manges[13] that the meningococcus is the sole etiologic agent in the Waterhouse–Friderichsen syndrome. The evidence that substantiates this claim is the increased prevalence of this syndrome during epidemics of meningitis and the frequent recovery of the meningococcus. This organism has been found in many isolated cases in which the etiology was obscure. The meningococcus was cultured in the 6 cases of the Waterhouse–Friderichsen syndrome encountered in this series. We strongly doubt the primary role ascribed to other microorganisms and support the concept that they represent secondary invaders.[13]

It is now a well-established fact that the meningococcus obtains its initial hold in the nasopharynx, from which it rapidly invades the blood stream. If adrenal hemorrhages occur, the classic picture of the Waterhouse–Friderichsen syndrome results and is manifested by bacteremia, shock and toxemia. Each of these factors forms the basis of a theory that attempts to explain the pathogenesis of this syndrome. It need scarcely be pointed out that the presence of bacterial organisms in the blood cannot per se adequately explain the adrenal hemorrhages and associated clinical evolution, because the Waterhouse–Friderichsen syndrome does not invariably follow every meningococcemia or other bacteremia. A further objection to the bacteremic theory is the failure in these cases to demonstrate pathologic lesions of a focal embolic type. Nor can shock alone explain the ensuing histologic picture. The major criticism of this concept and of the conclusions drawn is that observations were made in all instances on cases with brief clinical courses. Not until studies have been made on cases surviving the initial phase will one be justified in differentiating this early state of shock from the later and more fully developed toxemic state of hepatorenal failure. These studies have shown that the clinical features of shock, such as weakness, pallor, a thready pulse and low blood pressure, although present early in this syndrome, do disappear within six to eight hours, provided that the patient survives. No terminal fall in blood pressure was observed. Notwithstanding clinical recovery from shock, which in itself was variable in severity and duration, the alterations in the blood nonprotein nitrogen and creatinin continued to progress unfavorably. Furthermore, it was impossible to demonstrate hemoconcentration, hypochloremia or a fall in blood sodium and a rise in blood potassium, all of which are characteristic of shock. That the morphologic alterations in structure found in shock are strikingly similar to those found in the Waterhouse–Friderichsen syndrome cannot be questioned, but to attribute the pathologic changes in this syndrome to shock despite obvious clinical recovery from this state is untenable. Thus, the preponderance of evidence supports the principle of toxemia as the most important factor in the pathogenesis of the Waterhouse–Friderichsen syndrome. That shock may have been an early but temporarily associated factor in these cases cannot be denied. Rather, the emphasis must be placed on the toxins elaborated by the meningococcus, with its subsequent disorganization of the structure and function of the endothelial cells, and certain types of parenchymal cells. The endothelial cellular damage resulted in hemorrhages into the skin and adrenal glands, extravasation of fluid into the serous cavities and pulmonary edema. The parenchymatous changes, which were degenerative in nature and were found in the liver, kidneys and heart, resulted in hepatorenal failure.

In the previous publication, we[6] showed the existence of two stages in the Waterhouse–Friderichsen syndrome. The first or fulminating stage was characterized by a short course and circulatory collapse. The pathologic changes were cloudy swelling of the myocardium and an early hepatitis associated with adrenal hemorrhages. Death was most readily accounted for by shock subsequent to the overwhelming toxemia. The second or hepatorenal stage was found only in the patients who survived for longer intervals, and its main histologic features were cloudy swelling with fragmentation of the myocardium, adrenal hemorrhages, a severe and widespread necrobiosis of the hepatic cells and cloudy swelling of the renal convoluted tubular epithelium, together with avascularity and increased cellularity of the glomeruli. Death in these cases was attributed to hepatorenal failure.

We believe that adrenal hemorrhages are necessary for the development of the Waterhouse–Friderichsen syndrome, although it is difficult to explain their exact role. Investigators have shown that the adrenal cortex plays an important part in the maintenance of renal function and body resistance to toxic agents. It is therefore suggested that the destruction of adrenocortical tissues by hemorrhage results in a failure of renal function and increased sensitivity to the meningococcic toxin. The latter

may well account for the degenerative changes found in the liver, kidneys and heart.

Summary and Conclusions

A report is made of 6 cases of the Waterhouse–Friderichsen syndrome. Criteria for diagnosis based on an analysis of these cases are presented. A case of recovery is discussed in detail, and the literature on recovery in this syndrome is reviewed.

The following conclusions are based on a study of these cases

The clinical features are fairly constant. The significance of the renal failure as evidenced by the initial anuria followed by oliguria has heretofore not been fully appreciated.

The pathologic findings are uniform but vary in degree. All cases have macroscopic bilateral adrenal hemorrhages. Microscopically the changes in the heart, liver and kidneys are not conspicuous in the short-lived cases but are pronounced in those cases with relatively long clinical courses.

The roles of bacteremia and shock in pathogenesis have been overemphasized. Death in all cases is probably the effect of the overwhelming toxemia, which in the short-lived cases results in profound shock and in those with relatively long survival periods leads to hepatorenal failure.

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TRANSITORY LUNG INFILTRATIONS ACCOMPANIED BY EOSINOPHILIA

Report of a Case

Captain Henry Miller, M.C., A.U.S.

THE clinical aspects of any disease may be said to comprise a group of features that in the aggregate tend to classify it as a clinical entity. Some diseases have certain pathognomonic features that identify them immediately, whereas in others the clinical picture is simulated by such a variety of etiologic agents that it is impossible to be certain of the diagnosis except by careful study and the elimination of similar diseases. Such a condition is the syndrome of transient pulmonary infiltrations with blood eosinophilia, first described in 1932 by Loeffler,[1] professor of medicine at the University of Zurich. By 1940, 105 cases had been reported in the literature,[2] 51 of them by Loeffler.[3]

The most important criteria for diagnosis are the symptoms and signs of pulmonary disease, the extent and character of pulmonary involvement, the transient character of the pulmonary shadows, eosinophilia, and seasonal and sex variation. These will now be discussed. The symptoms as a rule are few, and the course is mild and invariably benign. The majority of patients do not appear to be acutely ill. Over 25 per cent of Loeffler's cases were discovered accidentally. There is rarely any appreciable rise of temperature. A cough, with or without chest pain and expectoration of frothy, mucoid sputum, may be present. Abnormal physical signs over the lungs are few, and in general consist of occasional moist rales. Sometimes impairment of the percussion note and changes in breath sounds are elicited. The sedimentation rate is usually increased.

X-ray examination usually reveals a more extensive pulmonary involvement than was suspected from the clinical examination. The characteristic x-ray picture described by Loeffler and also by Breton[4] consists of abnormal shadows that appear and disappear rapidly, only to reappear in another portion of the lung. The involvement varies in size and position. It occurs most frequently in the lower lung fields but may occur anywhere. It may be small or large, unilateral or bilateral, single or multiple and homogeneous or spotty. A fine, fibrous, star-shaped scar may be left after resolution. Occasionally there is a small pleural effusion, but it is never large enough to warrant thoracentesis. The pulmonary shadows decrease in size and density in three to eight days, and completely disappear within a few more days. Other shadows may appear in different regions of the lungs in rapid succession.

The eosinophilia usually ranges between 15 and 35 per cent, but has in some cases exceeded 60 per cent. It is associated with the lung shadows, but

Loeffler found no parallelism between the degree of eosinophilia and the extent of the infiltrations. There appears to be a definite seasonal variation, most cases being found in July and August; furthermore, males are more frequently affected than are females.

The pathology of this disease is unknown, since no clear-cut fatal case has come to autopsy. In 1939, Smith and Alexander[5] reported a fatal case of so-called "Loeffler's syndrome" in a seven-year-old girl. As brought out in the discussion, the high fever, stormy course, long duration and fatal outcome did not fit into the picture of a true Loeffler's syndrome. In addition, none of five nationally known pathologists could agree on the diagnosis. Terminal leukemia was granted by one and questioned by the other four.

The etiology of the disease is also uncertain. Most authorities describe the syndrome as an allergic response of the pulmonary tissue that may be induced by various allergens. Loeffler recognized the probable presence of multiple etiologic factors. Leitner[6] associated the condition with pulmonary tuberculosis. Wild and Loertscher[7] reported 2 cases of the syndrome in children infected with *Ascaris lumbricoides* and explained the pulmonary shadows as due to the passage of the larvae through the lungs. Engel[8] described a similar clinical picture of transient pulmonary infiltration and blood eosinophilia in himself and a friend, and attributed the condition to hypersensitivity to the pollen of the privet plant. In 1937, Meyer[9] reported 8 cases, including one that developed sudden rhinitis, conjunctivitis and edema of the face, accompanied by eosinophilia and lung infiltration. All these manifestations disappeared with calcium therapy and removal of contact to a pollen to which the patient gave a strongly positive reaction. Since then, other investigators have reported transient lung shadows in asthmatic patients and have decided that an allergic process is probably responsible for the entire picture. Although asthma is the most frequently associated allergic manifestation, other forms of allergy have been noted.

Stefano[10] reported a case of bronchial asthma in which transient areas of pulmonary infiltrations demonstrable by x-ray were associated with amebas in the sputum. Both the asthma and the amebas disappeared after emetine therapy. Hoff and Hicks[11] have also reported a case of Loeffler's disease associated with amebiasis. Quintana[12] described a case in which *Necator americanus* was present in the stools. Lavier, Bariety and Caroli[13] have described a case of pulmonary infiltration with eosinophilia in a case of infestation with *Fasciola hepatica*. In the great majority of cases, no etiologic agent has been found.

The following case is reported because of the apparent rarity of the condition. A review of the literature reveals but 4 such cases reported in this country.[2, 11, 14, 15]

Case Report

A 23-year-old soldier was admitted to the hospital on November 27, 1943. For several days prior to admission he had noticed unusual shortness of breath on moderate exertion. This was particularly evident when he ran up an embankment to his gun position. On November 26, he developed a sore throat, fever, generalized malaise and aching of the bones and muscles. On the morning of the 27th, he developed a shaking chill that lasted for 2 hours. On the day after admission, he developed a nonproductive cough associated with a dull, aching pain in the left side of the chest. He gave no history of hemoptysis, pleurisy or weight loss and no family history of tuberculosis. Careful questioning revealed nothing suggestive of allergy in the family or past history. There were no symptoms referable to the gastrointestinal or genitourinary system.

On admission, the temperature was 100°F., the pulse 84, and the respirations 20. The pharynx was granular and moderately injected. The lungs were resonant throughout. On auscultation numerous rhonchi were heard throughout both lung fields, being most marked at the bases posteriorly. No moist rales were noted. The area of cardiac dullness was not enlarged, the rhythm was regular, and no murmurs were heard. The aortic second sound was equal to the pulmonic. The blood pressure was 114/78. The abdomen was soft, and no organs or masses were felt.

The temperature dropped to normal in 24 hours, and the patient remained afebrile throughout the hospital stay. The pulse varied between 60 and 78, and the respirations were 20. On the 9th hospital day, the cough became productive of gradually increasing amounts of frothy, whitish, mucopurulent sputum, which eventually totaled 30 to 60 cc. a day. This persisted for 2 weeks and then gradually decreased, so that after 4 weeks the cough and expectoration of sputum ceased. On December 14, examination revealed diminished resonance at the right base, with numerous fine, moist rales at both lung bases posteriorly. The rales gradually decreased, and on December 31 the lungs were clear on physical examination. The patient did not appear acutely ill at any time, and treatment for the most part was symptomatic. He received two doses of 3 cc. each of tetrachlorethylene nd two courses of 1 gm. each of hexylresorcinol crystoids, following which the ova of *Trichuris trichiura* (see below) disappeared from the stools. On January 20, he was started on 0.015 gm. of Mapharsen; this was followed by biweekly injections of 0.06 gm. of the drug for ten doses.

Repeated urinalyses were normal. Concentrated specimens revealed no evidence of ova or parasites in the sediment. Thirty-two stool examinations were negative for the ova of *N. americanus, Schistosoma mansoni* and *A. lumbricoides* and cysts and trophozoites of *E. histolytica*. On January 18 and 26, an occasional ovum of *T. trichiura* was found in the stool. Twenty-six sputum examinations revealed no evidence of tubercle bacilli, fungi, ova or parasites; a culture revealed *Staphylococcus aureus*. From December 9 to 18, examinations revealed a moderate to marked increase of eosinophils in the sputum.

Tuberculin tests were negative. An electrocardiogram was normal. Between January 13 and 15 the patient was skin-tested with twenty-four common allergens, with completely negative results. A sigmoidoscopic examination to a depth of 37 cm. revealed the bowel mucosa to be normal throughout, no hemorrhagic areas being seen. Agglutination tests and the brucellergen intradermal test for brucellosis were negative. An intradermal test with trichinella antigen was likewise negative.

Numerous thick blood films were negative for malarial and other parasites. Three midnight blood smears were negative for filariasis. Repeated examinations of blood smears revealed no abnormality of the erythrocytes. The eosinophils in the blood varied from 64 to 85 per cent during the first two months and had returned to normal (2 per cent) at the end of the third month (Table 1). The eosinophils were adult if judged by the nuclei, which were multilobed. On December 27, smears of the sternal marrow revealed it to be predominantly myeloid, and the elements present were of the

late stages of the myelocytic series. There was a distinct increase in the number of eosinophils.

On November 28, radiographic examination of the chest revealed increased hilar markings, with multiple small areas of increased density scattered through both lung fields (Fig. 1). On December 10, the x-ray films revealed resolution of the previously reported process, but an area of infiltration was present in the lower lobe of the right lung (Fig. 2). On December 26, there was almost complete resolution of the pneumonic process at the right base, with some residual thickening of the interstitial structures in this region (Fig. 3). A film on January 9 revealed clear lung fields. X-ray films of the skull and the long bones revealed no abnormalities.

The patient eventually returned to active duty.

Table 1. *Summary of Hematologic Findings.*

Date	Hemoglobin	Red-Cell Count	White-Cell Count	Differential Count				Sedimentation Rate (Westergren)
				Neutrophils	Eosinophils	Lymphocytes	Monocytes	
	%	$\times 10^6$	$\times 10^3$	%	%	%	%	mm.
11/29			16.2	7	85	8		
12/2			18.8	10	76	14		
12/10			19.9	11	79	10		58
12/13	90	4.7	30.8	14	76	10		
12/16			24.7	11	76	13		
12/20								77
12/23			41.0	17	80	3		55
12/26			33.0	10	79	11		
12/29	95	5.0	27.7	11	82	7		
1/2			25.8	6	82	12		
1/7	90	4.5	21.1	17	64	19		
1/14			19.5	9	75	14	2	
1/17	85	4.25	19.6	14	76	10		65
1/21			21.9	14	69	17		
1/25			19.6	12	79	9		
1/31			22.5	11	72	16	1	
2/5	90	4.42	12.1	12	61	27		61
2/8			7.0	20	58	21	1	
2/13			6.7	31	36	33		
2/17			6.2	44	31	25		
2/24	105	4.95	5.6	76	2	20	2	15

Figure 1.

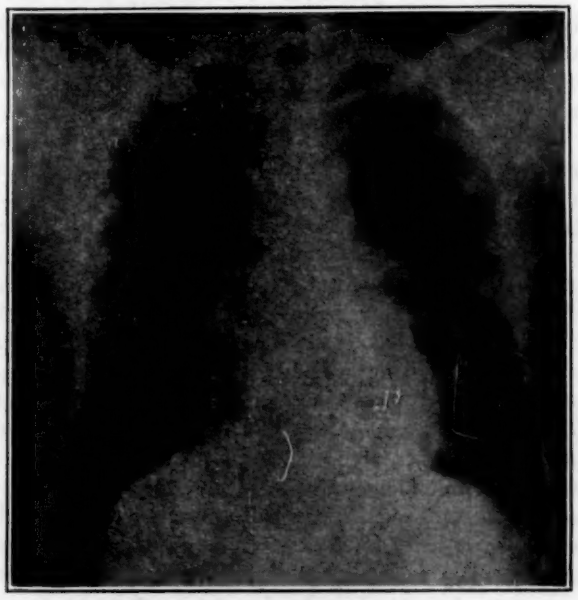

Figure 2.

Discussion

With regard to the differential diagnosis, it is to be noted that periarteritis nodosa[16] and Hodgkin's disease[17] may at times be associated with a hypereosinophilia, but in the present case these diseases can be definitely excluded by the clinical course. There was no means of ruling out familial eosinophilia.[18] There is a group of unusual cases with varying symptoms reported as "eosinophilic leukemia," but this disease resembles a genuine leukemia in that the spleen is greatly enlarged, the number of leukocytes is markedly increased, there is a tendency to hemorrhage, and the outcome is uniformly fatal.[19] In 1931, Bass[20] reported a case that was diagnosed as eosinophilic leukemia. X-ray examination revealed generalized speckled shadows throughout both lung fields, which suggested miliary

infiltration. These findings were not transitory. Repeated examinations over a period of six months revealed no significant changes. Diffuse pulmonary infiltration, fever and eosinophilia have been reported in chronic brucellosis,[21] but in the present case the agglutination reaction and a skin test for brucellosis were negative. Trichinosis, which may have respiratory abnormalities as a significant feature of the disease,[22] is rare in this locality, and could be excluded by the clinical course and negative skin test.

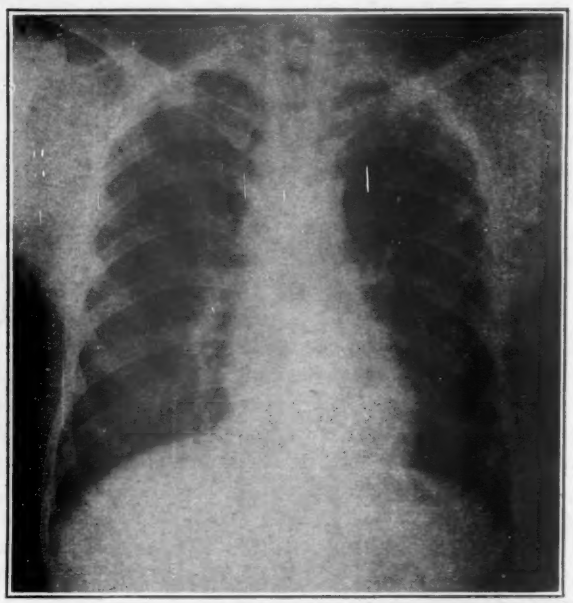

FIGURE 3.

Other tropical diseases characterized by blood eosinophilia were excluded by clinical and laboratory studies. Although trichuriasis may at times be associated with urticaria and a moderate eosinophilia, it is doubtful whether it was a significant etiologic factor. Recently, Weingarten[23] in India described what he believes to be a new clinical entity, manifested by severe, paroxysmal bronchitis and a high eosinophilia, in which arsenicals are a specific and quickly acting remedy. The disease is characterized by a paroxysmal cough, expiratory dyspnea and occasional attacks of bronchial asthma, with mucopurulent sputum often containing clumps of eosinophils. A low-grade fever, a moderately enlarged spleen, an eosinophilia up to 88 per cent and a moderately accelerated sedimentation rate are usually present. X-ray examination reveals disseminated mottling of both lungs, indicating small bronchopneumonic infiltrations. Although benign, this disease may last for several years. Arsenicals are specific, and the eosinophilia disappears rapidly after several injections. This paper was the basis for the treatment of our patient with Mapharsen.

The case reported appears to be typical of the Loeffler syndrome in that the condition was benign, there was practically no elevation of temperature, the pulmonary infiltration shifted during the course of the disease, and a marked peripheral eosinophilia was present.

SUMMARY

A case of Loeffler's syndrome is presented. The eosinophilia was more marked than it has been in the majority of reported cases, and appeared to respond to treatment with Mapharsen. No definite etiologic agent was found.

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MEDICAL PROGRESS

THE PORPHYRINS*

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THE average physician confronted with the subject of porphyrin metabolism pictures either a bewilderingly complex group of strange pigments obtained from stools and urine or an exceedingly rare disease characterized by sensitivity to light and acute abdominal pain. Actually, porphyrin derivatives are an essential part of the respiratory enzymes present in all living cells, and an understanding of their nature and relations may be expected to lead to improvement in the diagnosis and treatment of many human diseases. It is the purpose of this paper to discuss one of these porphyrins, protoporphyrin, and to indicate the role it plays in normal and abnormal human metabolism.

PROTOPORPHYRIN

The important chemical and physiologic roles of the substance protoporphyrin concern its integration into the iron-containing enzymes and pigments. Heme or hematinlike substances are formed when iron enters the center of the protoporphyrin ring, and the heme group combines with various specific proteins to form compounds such as blood hemoglobin, muscle hemoglobin, catalase, peroxidase and the cytochromes. These are essential and widely distributed substances in the body, and their specific physiologic or enzymatic functions are determined by the type of protein attached to the heme group. Although the heme group does not determine the specific function, it is nonetheless important as a common denominator of this whole group of substances. As compared with its appearance in these iron compounds, protoporphyrin free of iron and protein does not occur in large amounts in the body. It is present largely in the young cells of the red-cell series in the bone marrow and the peripheral blood.

Protoporphyrin was first found to be an iron-free derivative of hemoglobin by Kämmerer[1] in 1923. He demonstrated this by diluting blood with broth and inoculating it with fecal bacteria and putrid material from gangrenous lesions and bronchiectatic cavities, and incubating it for four to six days. Hoagland[2] had shown in 1917 that sterile autolysis of muscle resulted in a pigment identical with protoporphyrin, which by further hydrolysis changed into hematoporphyrin. In 1924, the porphyrin present in natural hemin was crystallized and was shown by Fischer[3] to be protoporphyrin. Other studies followed.[4–7]

Protoporphyrin occurs in feces as a bacterial decomposition product of hemoglobin, and is chiefly exogenous.[8–10] Formation also takes place by bacterial decomposition of different types of tissue, such as the calf's heart and the liver, lung and uterus of various species.[5] Protoporphyrin 9 has been found in sheep liver by Rimington.[11] Excluding the above sites, the distribution of protoporphyrin in nature is somewhat bizarre. It is found in large amounts in the Harderian gland of the rat family.[12] It is apparently an excretion product of this gland, and none is produced for utilization in the animal. Protoporphyrin occurs as a pigment of the egg shells of certain birds, such as the plover, that nest in the open.[13] It has been found in incubated hens' eggs.[14] It is present in alkalized yeast, in plants such as peas, corn and beans and in the leaves of the ash and the maple.[15–19]

RELATION OF PROTOPORPHYRIN TO OTHER PORPHYRINS

Considerable knowledge of the structure and chemical properties of the various porphyrins exists, but the physiologic relations are rather obscure. All the porphyrin compounds consist of a basic porphyrin ring made up of four pyrrol groups attached to each other by methene linkages. The identity of a particular porphyrin is the result of the type and position of radicals attached to eight substitution points along the porphyrin ring. Porphyrin compounds in the body fall into two groups — first, those having four each of two different radicals in the eight substitution points along the porphyrin ring, and second, those having three radicals divided into four of one type and two each of the others. The first group has four possible isomers and the second has fifteen.

Examples of the first group are coproporphyrin and uroporphyrin. Both have four of two different types of radicals attached to the porphyrin ring. The four isomers that any porphyrin in this group may conform to are termed "types" and are numbered from 1 to 4. Only Types 1 and 3 are found

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in nature. Types 2 and 4 do not occur naturally but have been synthesized. Types 1 and 3 are shown in Figure 1.

Porphyrins of the second group are characterized by three different radicals substituted and fifteen isomers; in this group are included deuteroporphyrin, mesoporphyrin, hematoporphyrin and protoporphyrin. Each of the fifteen isomers conforms to one of the four types in the first group of simpler porphyrins. Examples of these compounds are shown in Figure 2.

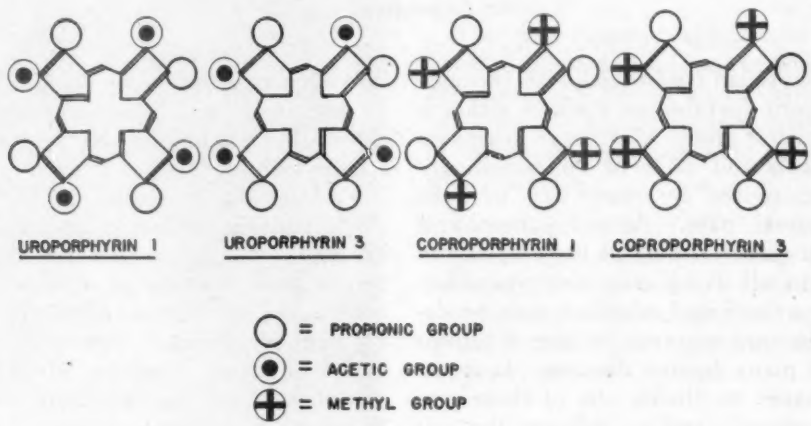

FIGURE 1.

The uroporphyrins and coproporphyrins are more carboxylated than protoporphyrin or the other more complex porphyrins. If the two vinyl groups of protoporphyrin are saturated and a carboxyl group is added, it is transformed into coproporphyrin. If, further, coproporphyrin has the four methyl groups altered and carboxylated to acetic groups, a transformation to uroporphyrin takes place. The question arises whether such a carboxylation occurs in the body and whether the simpler porphyrins are excretion products of protoporphyrin.

Before an attempt is made to answer this question, certain important concepts concerning the relations of the porphyrins should be discussed. The first concept is a phenomenon described by Fischer and Orth[20] and called by them "the dualism of the porphyrins." By this is meant the constant appearance in the body of two isomer types as the result of concurrent independent synthesis. It is considered impossible for the two types to merge or interchange unless there is a breaking up of the stable porphyrin ring and a resynthesis. This is extremely unlikely. Thus, a Type 1 porphyrin may be formed from, or changed into, other Type 1 compounds, but it is impossible for either type to change into the other. When there is found in the organism a highly specialized porphyrin such as protoporphyrin 9, a Type 3 compound, it follows that if this substance has porphyrin precursors or derivatives, these must also be Type 3 porphyrins. According to this hypothesis uroporphyrin 1 and coproporphyrin 1 could never be incriminated as precursors or derivatives of Type 3 protoporphyrin.

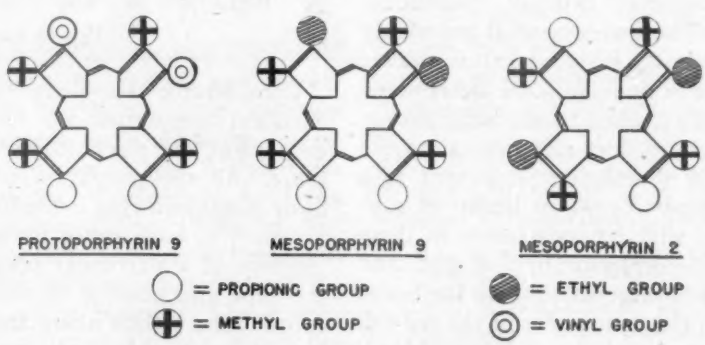

FIGURE 2.

A second concept consists of Rimington's[21] theory of "enzymatic control," partial credit for which should be given to Dobriner.[22] Rimington has hypothesized that a ratio exists between the Type 3

and the Type 1 series of porphyrin compounds in the body, this ratio being greatly in favor of the former. The explanation lies in the hypothetical formation of porphyrins from two dissimilar dipyrromethenes, — each one half a porphyrin ring with suitable radicals attached, — which may be designated as X and Y. The radicals of the dipyrromethenes are arranged so that when X and Y unite a porphyrin such as protoporphyrin 9 (Type 3) is formed. This reaction is controlled by enzymes, but a small fraction of X molecules combine with other X molecules to form a Type 1 porphyrin. It would be reasonable to expect that a small fraction of dipyrromethene Y molecules would combine with each other to form a Type 2 porphyrin, but

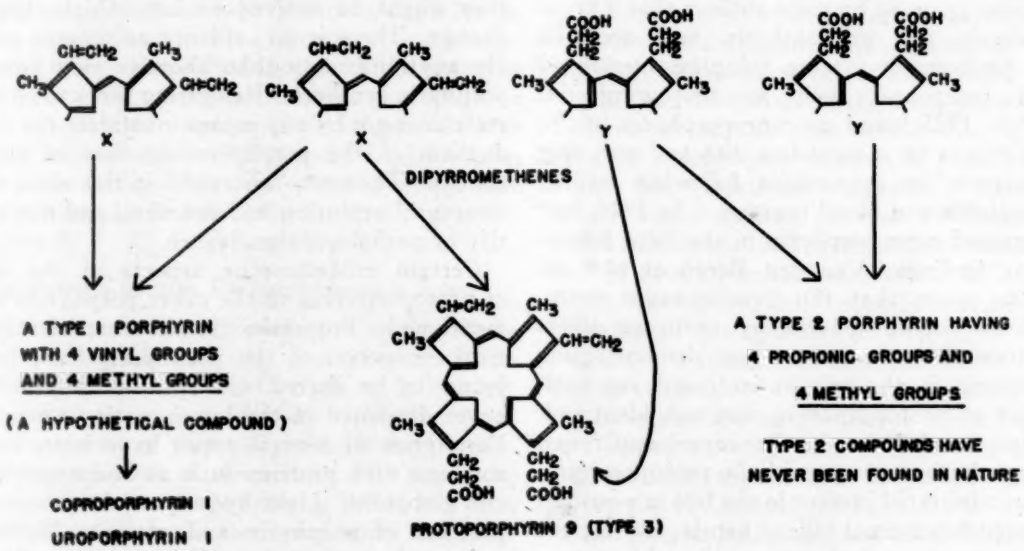

FIGURE 3.

none of this has ever been found in nature or the body. This discrepancy has been anticipated by postulating that the only leak in the reaction centers around the combination of similar X molecules, the enzyme system entirely preventing the combining of Y molecules. The whole reaction is theoretically tenable and can be expressed structurally as shown in Figure 3. These theories furnish a convenient explanation for the presence of uroporphyrin and coproporphyrin 1 in the body as breakdown products either of Type 1 protoporphyrin or of some other as yet undiscovered complex Type 1 porphyrin. Another theory presupposes that uroporphyrin 3 and coproporphyrin 3 are formed directly from dipyrromethenes and that the Type 1 analogues occur as an artefact of their synthesis.

The occurrence of porphyrins in the diseased and normal body should be briefly summarized in a search for facts correlating with these theories. Besides protoporphyrin only coproporphyrin and uroporphyrin and their isomers occur in the body if mesoporphyrin[23,24] and deuteroporphyrin[25–27] are excluded as exogenous in the feces. Vigorous investigation of uroporphyrin and coproporphyrin has revealed few generalizations. Uroporphyrin and coproporphyrin are found largely in the urine and feces.[28] Coproporphyrin is considered the only porphyrin normally present in urine.[29,30] Some authorities[31] report that normal bile contains coproporphyrin 1, and other investigators[32] find no coproporphyrin in bile. When an increase of uroporphyrin or coproporphyrin occurs in disease, the normal liver causes Type 1 porphyrins to be excreted in both the urine and the bile, but Type 3 isomers of these substances are excreted exclusively in the urine.[28] Coproporphyrin excretion in the urine and the urinary fecal ratio have been thought to be sensitive tests of hepatic function,[28] but this is not so.[33]

In diseases characterized by marked increases of uroporphyrin and coproporphyrin there has never been found any abnormality of the protoporphyrin metabolism. Such diseases are known as porphyria if they are due to inborn errors of metabolism or as porphyrinuria if secondary to other diseases. Congenital porphyria has the clinical features of photosensitivity, red teeth and bones and dark-red or brown urine.[34] Uroporphyrin 1 and 3 are deposited in the skeleton, and Type 1 isomers of uroporphyrin and coproporphyrin are found in large amounts in the urine. Acute porphyria is associated with acute episodes of abdominal cramps, neurogenic paralyses and mental symptoms, and also with dark urine.[35] The urine contains large amounts of Type 3 uroporphyrin and coproporphyrin. No involvement of protoporphyrin has been found to occur in these

diseases, and there are present no marked anemias that might be attributed to an error in the formation of protoporphyrin. Applying the theory of enzymatic control to congenital porphyria, the increases of Type 1 porphyrins could be interpreted as a lack of the normal retardation of these compounds, resulting in an abnormal ratio between the Type 1 and Type 3 porphyrins. No protoporphyrin 1 has ever been reported in patients with this disease.

The porphyrinurias are diseases in which the excess of porphyrin is usually coproporphyrin of either type secondary to other disease, such as liver disease,[36] pellagra,[37] febrile conditions[38] and diseases of the blood-forming organs. Protoporphyrin has never been involved, except in diseases in which anemia exists, which will be treated under a separate heading.

It has been assumed by most authors that Type 3 coproporphyrin and uroporphyrin may well be excretion products of a more complex, specialized porphyrin compound such as protoporphyrin. Schumm[39] in 1923 found no coproporphyrin in the urine of patients on a meat-free diet and was able to demonstrate its appearance following feeding with hemoglobin and blood sausage. In 1926, he[40] found increased coproporphyrin in the feces following similar feedings. Van den Bergh et al.[41] attempted to prove that the liver changes protoporphyrin to coproporphyrin by perfusing livers with protoporphyrin solutions and demonstrating coproporphyrin in the bile in increased amounts. The isomer of protoporphyrin was not identified. Vigliani and Sonzini[32] in a similar experiment found no coproporphyrin and most of the protoporphyrin that was administered present in the bile in a patient with a complete external biliary fistula. By far the most conclusive investigations on this subject were those of Watson, Pass and Schwartz,[42] who repeated and modified van den Bergh's experiments. Only increases of Type 1 coproporphyrin were demonstrable, and these increases, although distinct, were small and represented only a fraction of the administered protoporphyrin. It is impossible for coproporphyrin 1 to be a direct product of protoporphyrin 9, so that to explain the increase of the latter it must be hypothesized that protoporphyrin stimulates synthesis of coproporphyrin 1 in some unknown fashion.

The hypothesis of so-called "dualism of the porphyrins" would be immeasurably strengthened if it could be demonstrated that small amounts of a Type 1 protoporphyrin are present in hemoglobin along with the usual Type 3 protoporphyrin. This would establish a highly specialized functioning end product of the Type 1 series of porphyrins and afford a substance from which coproporphyrin and uroporphyrin 1 could be reasonably derived. When Fischer[43] in 1939 described experiments identifying a small fraction of natural hemoglobin as containing protoporphyrin 2, a Type 2 compound, wide interest was aroused and the matter was considered as solved. His experiments depended on the transformation of protoporphyrin to mesoporphyrin, with esterification and identification of the latter. However, in a second, obscurely titled paper, Fischer and Schroder[44] retracted the earlier findings on the identification of mesoporphyrin 2 (Type 1) as a derivative of the hemoglobin of normal blood. Conversions of the supposed mesoporphyrin 2 to rhodins and verdins showed no trace of mesorhodin 2 or mesoverdin 2. The conclusions of these workers were that no protohemin 2 (Type 1) exists in normal blood.

These facts change considerably the attitude toward the Type 1 porphyrins, uroporphyrin and coproporphyrin. There are no other Type 1 porphyrin compounds known in the body from which they might be derived or into which they might change. There is no evidence at present that they are anything more than abortive side products of porphyrin synthesis. Relegating them to an abortive state does not by any means invalidate the theory of dualism of the porphyrins or that of enzymatic control. The term "abortive" in this sense refers to structural evolution and function, and not to quantity or pathologic significance.

Certain miscellaneous aspects of the relations of protoporphyrin to the other porphyrins must be mentioned. Properties of photosensitization common to several of the porphyrins have not been found to be shared with protoporphyrin.[28] It is never deposited in the bones, as is uroporphyrin.[45] Porphyrins of several types have been known to combine with proteins such as fibrinogen, albumin and globin.[46,47] Light hydrolyzes the proteins in the presence of porphyrin and oxygen. Fischer[48] has suggested a correlation of the toxicity of the porphyrins with the number of carboxyl groups present in each. The order of toxicity as judged by the production of light shock in mice is as follows: hematoporphyrin 9, Type 1 uroporphyrin, deuteroporphyrin 9, Type 1 coproporphyrin and protoporphyrin 9; Type 3 coproporphyrin is only slightly toxic, and uroporphyrin 3 is nontoxic.[28]

Precursors of Protoporphyrin

The steps in the formation of protoporphyrin in vivo are unknown. In 1929, Fischer[49,50] synthesized heme from simple pyrrols. Dipyrromethenes were formed from pyrrols and then condensed to a Type 3 porphyrin that in a series of steps became protoporphyrin 9. In the body Fischer[20] has suggested simpler sources, such as proline, oxyproline and tryptophane. Dipyrromethenes probably form a step in the synthesis. There are two clues to the presence of dipyrromethenes in the body — the pentdyopent reaction and the porphobilinogen test. In neither of these reactions has a dipyrromethene been shown to exist free inside the body. The pentdyopent reaction consists of a spectroscopic

absorption band appearing at 525 millimicrons when hemoglobin, heme, bilirubin or urobilin solutions are treated with hydrogen peroxide, particularly in alkaline solution in the presence of sodium hydrosulfite.[20] Fischer and Stern[51] have identified the substance producing the absorption band as a dipyrromethene. The relation of protoporphyrin to the pentdyopent reaction is mentioned only twice in the literature. Hulst and Grotepass[52] state that pentdyopent may be prepared from protoporphyrin, although the oxidative process is much slower. Fischer and Müller[53] report that none of the porphyrin compounds, including protoporphyrin, give the pentdyopent reaction. The porphyrin ring can be readily broken down to the dipyrromethenes found in the pentdyopent reaction if iron and globin are attached or if it has already been broken down to a straight chain of four pyrrol groups, as in bilirubin or urobilin.

Porphobilinogen was first noted in the urine as the substance in porphyria that gave a positive Ehrlich reaction not due to urobilinogen. It was discovered by Waldenström[54] in 1937. It is considered to be a dipyrromethene, and a simple test for it has been devised and the literature reviewed by Watson.[55]

Breakdown of the Protoporphyrin Ring

This subject is intimately tied up with the breakdown of hemoglobin and the iron enzymes. The probability of breakdown through uroporphyrin and coproporphyrin has already been discussed. The vast majority of protoporphyrin in hemoglobin is broken down and eliminated as bile pigments, and degradation to porphyrins is minimal. Iron does not separate from the heme until the porphyrin ring has been split open,[56,57] thus avoiding a free porphyrin stage.

In 1935, Schreus and Carrié[58] reported the formation of protoporphyrin by the action of ground-up liver on hemoglobin at 36 to 60° C. They believed that the effect was due to an enzyme that they called "hemase," and considered the formation of protoporphyrin intermediate in the breakdown of hemoglobin to bile. When the reaction was alkaline, bile formed, but this occurred at a higher maximum temperature, attributed by them to the possible destruction of catalase. These findings have never been confirmed, but if true are of great importance. Evidence militates against such a process predominating in vivo because of Lemberg's[56] demonstration that in hemoglobin the porphyrin ring is split open prior to the departure of the iron.

Red Cells and Hemoglobin

Protoporphyrin was first found in red cells by van den Bergh and Hyman[59] in 1928. Grotepass[60] isolated it and identified it as a Type 3 porphyrin. The association of protoporphyrin and reticulocytes was noted by two different groups. Watson and Clarke[61] ingeniously showed that most of the protoporphyrin is contained in the reticulocyte-rich stratum of centrifuged cells. They were also able to show that protoporphyrin is mutually precipitable with certain stains, such as cresyl blue, that stain reticulocytes. The precipitated protoporphyrin-dye substance microscopically resembles the framework of reticulin in reticulocytes, but the precipitation phenomenon is probably due to a buffering effect and not to the formation of an actual compound between the protoporphyrin and the dye.[62] De Langen and Grotepass[63] arrived at similar conclusions concerning the large amount of protoporphyrin in reticulocytes. Seggel[64,65] presents evidence that the erythrocyte protoporphyrin resides in cells called "fluorescytes," which can be identified only by their fluorescence in ultraviolet light. These cells normally occur in largest numbers in the bone marrow, their appearance and increase in the peripheral blood being associated with conditions causing reticulocytosis. Seggel has pointed out that fluorescytes appear later and decline more slowly than do reticulocytes in cases of pernicious anemia under liver treatment. Watson's[62] latest studies reveal a discrepancy between erythrocyte protoporphyrin levels and reticulocyte percentages in treated cases of pernicious anemia. This casts some doubt on whether all reticulocytes contain large amounts of protoporphyrin. To explain this discrepancy Watson has mentioned the possibility that in the peak of the reticulocyte response following liver therapy in pernicious anemia there may be a large number of reticulocytes that have had a megaloblastic origin and do not contain much protoporphyrin. Incubation of red cells for twenty-four to forty-eight hours resulted in a decrease of the reticulocytes but an increase of protoporphyrin. When experimental phenylhydrazine anemia was produced in rabbits, the protoporphyrin in red cells more nearly paralleled the reticulocytes than in pernicious anemia. Reticulocytes derived from megaloblasts would presumably not be present in the phenylhydrazine anemia.

The status of protoporphyrin in the bone marrow is not entirely clear. Borst and Königsdorffer[66] found it in normal marrow and increased in certain conditions, notably pernicious anemia. It was contained largely in erythroblasts and megaloblasts and occurred in the megaloblasts in pernicious anemia. It is generally conceded that the bone marrow contains large amounts of protoporphyrin in pernicious anemia,[32,38] but there is a difference of opinion about its presence in megaloblasts. Seggel and his co-workers were unable to find it there before or after treatment. Stasney and McCord[67] found protoporphyrin in megaloblastic marrow, but the amount increased as the marrow became normoblastic.

Lead poisoning has been found by Vigliani and his co-workers[68,69] to give rise to high protoporphyrin

levels in the red cells and plasma. This disease has long been associated with increased amounts of coproporphyrin 3 in the urine. In most diseases showing hyperactive erythropoeisis it is coproporphyrin 1 that is found in abnormal amounts. This finding is so regular that the presence of coproporphyrin 1 in the urine is said to be an index of increased erythropoeisis. In pernicious anemia coproporphyrin 1 has been found increased in the urine and plasma in relapse.[31,32] Rimington[70] has shown that coproporphyrin 3 predominates in the urine following sulfanilamide treatment. Both Rimington and Watson[71] have hypothesized that lead and sulfanilamide may interfere with the introduction of iron into the porphyrin molecule, resulting in the formation and excretion of coproporphyrin 3. Very few other investigations of protoporphyrin in diseases of the blood have been made except for Watson's[62] preliminary studies employing the photoelectric method, which showed moderately elevated levels in several diseases associated with reticulocytosis.

Peripheral red-cell protoporphyrin should probably be considered as a supply of one of the building blocks of hemoglobin. Increased supplies in the peripheral blood occur in conditions characterized by rapid formation of red cells in the marrow and the premature throwing off of some forms of young red cells into the circulation. The factors governing the release of these cells from the bone marrow apparently regulate the peripheral blood-protoporphyrin level. Such factors include the pathogenesis of the particular anemia, depletion of the peripheral red cells and the ability of the bone marrow to regenerate young forms. Increased protoporphyrin levels are probably secondary to these conditions. The temptation must be resisted to consider that in pernicious anemia there is an arrest of protoporphyrin synthesis, with resumption of this synthesis manifested by the increased protoporphyrin following the administration of liver extract.

Protoporphyrin in Urine

In kidneys perfused with various porphyrins, Grotepass and Hulst[72] reported that uroporphyrin was excreted rapidly by the kidney, coproporphyrin less so, and protoporphyrin not at all. In spite of the vast quantity of research done on urinary porphyrins, there has been only one report of protoporphyrin in the urine. Boas[73] in 1933 reported finding protoporphyrin in the urine of diabetic patients with jaundice, cholelithiasis, carcinoma of the gall bladder and other conditions. He used the ordinary ether-acetic and hydrochloric acid extraction methods. All other observers are in complete agreement that protoporphyrin has never been found in urine. No protoporphyrin has ever been reported in the hemoglobinurias or myoglobinurias or following the breakdown of red cells in the urine, as in hematuria.

Protoporphyrin in Enzymes

Fischer and Orth[20] have reviewed the early work on the identification of Type 3 porphyrins in enzymes and pigments. The more recent studies have been covered by Sumner and Somers.[74] The porphyrin in myoglobin was identified by Schönheimer[75] in 1929 as protoporphyrin. In spirographis hemin the porphyrin present is Type 3 protoporphyrin.[12]

Although not an oxidase, catalase is classified with the oxidases because of its structural similarity to them and because of its close connection to physiologic oxidation. It occurs in all forms of life except a few micro-organisms, and its action consists of protecting living things from hydrogen peroxide. Zeile and Hellström[76] showed that catalase is a hematin compound. Later, Stern[77] demonstrated that the hematin of catalase is protohematin 9. The highest concentrations are in the erythrocytes and liver.

Another important enzyme, peroxidase, occurs in all plant cells, although its occurrence in animals is problematical. It catalyzes the oxidation of large numbers of phenols and amines in the presence of hydrogen peroxide. Theorell[78] demonstrated it to be a hematin-protein compound. Verdoperoxidase, so called because of its color in the dry state, has a similar action and occurs to the extent of 1 per cent in white blood cells.[74] It contains 0.1 per cent iron and is assumed to be a heme-protein compound.

Cytochrome is widely distributed in nature and in the body. The bulk of investigation has been on cytochrome C because Types A and B are extremely labile. Cytochromes probably function as carriers of electrons and thus participate in complicated reactions leading to the removal of hydrogen from metabolites and the formation of water. Cytochrome C is a hematin-protein compound whose heme group differs from protoheme in having a tertiary-ring base condensed around it. It is bound to protein by two histidine-imidazole groups attached to iron on either side of the flat hematin disk and by thioether bindings to the ethyl groups (the ethyl groups taking the place of the usual vinyl radicals).[79,80] These bindings to the protein explain why cytochrome is not auto-oxidizable, since oxygen cannot approach the iron; for the same reason, cytochrome cannot unite with carbon monoxide or cyanide at ordinary pH values.

The isomer of protoporphyrin has not been identified in the case of all the iron enzymes. No such exhaustive study has been made on any of the enzymes as that by which Fischer excluded the presence of protoporphyrin 2 (Type 1) in blood. In the review of these compounds it can be seen that protoporphyrin and iron appear to be inseparable in any physiologic role, and that they are combined with a protein. A generalization can probably be made that neither protoporphyrin alone nor iron occurring alone, as in hemosiderin,[81] have any useful function or physiologic role.

Miscellaneous Studies Concerning Protoporphyrin

According to Hinsberg and Rodewald,[82] administration of protoporphyrin and hematoporphyrin to various animals resulted in an increased melanophore-distributing hormone of the hypophysis. The injected animals formed a substance inactivating this hormone, and the authors associate this inactivating agent with the serum of cancer cases. Hinsberg[83] also reported premature follicle formation in the ovaries of mice following injection of protoporphyrin and hematoporphyrin.

Chemical Aspects of Protoporphyrin

Fischer and Orth[20] have described the physical and chemical properties of protoporphyrin. It has been crystallized in two forms, and the crystals are usually yellow to reddish. It is soluble in chloroform, pyridine and ether, in acetic and hydrochloric acids and in aqueous solutions of alkalies. It is reddish in solution, like the other porphyrins. All the porphyrins produce intense absorption bands in the visible spectrum. The number and position of the bands vary with the pH, the temperature and the solvent, but under standard conditions the bands are characteristic for a given compound, all isomers having the same bands. A listing of the differentiating absorption bands of the porphyrins cannot be found in the English literature. Table 1 is modified from Vannotti.[38]

Protoporphyrin is differentiated from the other porphyrins by its spectroscopic bands, by the melting points of its methyl esters, by its solubility in sodium hydroxide and by its hydrochloric acid number. The hydrochloric acid number is the concentration in percentage of hydrochloric acid that, when shaken with equal parts of ether, removes two thirds of the porphyrin from the ether. Dobriner[28] gives a table of these constants that is taken from Fischer and Orth.[20]

The fifteen isomers of protoporphyrin have not yet been separately synthesized, but Fischer and Orth[20] have synthesized twelve of the fifteen isomers of mesoporphyrin. Protoporphyrin and its methyl ester are unstable, particularly in the presence of light, and for isomeric or quantitative determinations it is customary to convert the protoporphyrin to mesoporphyrin and form the methyl ester of the latter. The esters of all the porphyrins crystallize more easily than do the porphyrins themselves, and the ester melting point is more distinct. Watson[84] has recently summarized the methods of conversion of protoporphyrin to its methyl ester, and has added an improved micromethod involving the reduction of hydriodic acid, acetic acid and ascorbic acid.

Protoporphyrin can be prepared in many different ways,[1,2,85] but the most convenient method is that of Fischer and Pützer,[86] whose description of it has never been translated into English. This method is as follows:

> Six grams of hemin are heated to boiling with 300 gm. of formic acid of specific gravity 1.22. Six portions of 1 gm. each of finely powdered iron (specifically, "Kahlbaum for analysis") are introduced at five-minute intervals into the boiling liquid and boiled for fifteen more minutes after the last has been added. To avoid bumping it is necessary to shake the apparatus in a machine. After the total time reaction of forty minutes the entire hemin is transformed into porphyrin. It is then cooled off and filtered from the iron and the formed ferroformate. Protoporphyrin is precipitated by diluting with two to three volumes of water and adding solid ammonium acetate. The precipitate is freely washed with water and dried. In the filtrate there remains a small amount of protoporphyrin and much iron.

Grinstein and Watson[87] have recently reviewed the methods of purification of the crude product and have modified Hamsid's method. The protoporphyrin is dissolved in a small amount of chloroform, and petroleum ether is added until a precipitate begins to form; crystallization is completed in an icebox. Further purification occurs on forming the dimethyl ester, and Watson[87] has devised a method of purification of the ester using chromatography and eluting a chloroform-dissolved ester with

Table 1. *Absorption Bands of Porphyrins in Various Solvents.*

Porphyrin	Solvent	Absorption Bands							
Protoporphyrin	Hydrochloric acid (25 per cent)*	602,4	582,2	557,2					
	Hydrochloric acid (25 per cent)†	602,7		557,2	410,8				
	Potassium hydroxide (N/10)*	645,2	591,0	539,7					
	Potassium hydroxide (N/10)†	642,0	591,0	540,0					
	Ether*	632,5	585,1	575,8	536,8	501,9			
	Chloroform†	630,6		575,3	540,7	506,9			
	Pyridine†	632,8		576,0	541,0	507,0			
Protoporphyrin dimethyl ester	Hydrochloric acid (25 per cent)*	668,8	603,4	583,4	557,0				
	Chloroform*	631,6	603,9	581,1	541,3	506,0			
Hematoporphyrin	Hydrochloric acid (25 per cent)*	595,8	575,5	551,7	527,9	510,5			
Mesoporphyrin	Hydrochloric acid (25 per cent)*	593,1	572,4	548,7	524,8	508,7			
	Ether*	623,3	612,4	596,6	578,3	567,6	559,0	528,6	494,6
	Chloroform†	621,0				565,9		532,8	498,2
Coproporphyrin	Hydrochloric acid (25 per cent)*	593,6		550,2	405,8				
	Hydrochloric acid (25 per cent)*	593,6	574,6	550,9					
	Ether†	623,6	568,4	526,3	495,0				
	Pyridine†	622,5	567,5	531,5	499,5				
Uroporphyrin	Hydrochloric acid (25 per cent)*	596,6	577,6	553,6	511,3				
	Hydrochloric acid (25 per cent)†	597,1		554,1		410,7			
Deuteroporphyrin	Hydrochloric acid (25 per cent)*		591,5		548,5				
	Hydrochloric acid (5 per cent)*		589,5	569,0	546,6				
	Ether*	621,7	595,7	576,8	566,8	525,9	494,1	430	

*According to Fischer.
†According to Schumm.

petroleum ether.[37] A method of transformation of protoporphyrin to protohemin is described by Fischer and Pützer[86] in which ferrous acetate or ferric chloride is allowed to combine with protoporphyrin, depending on whether divalent or trivalent iron is to be added.

Grinstein and Watson[88] review the older methods of extraction of free protoporphyrin from blood cells and present a new modification. Previous methods used spectroscopic or fluorometric determinations of the protoporphyrin. Watson's method employs the photoelectric colorimeter's measurement of the absorption of light at 400 millimicrons, the maximum absorption band of protoporphyrin being at 407 millimicrons. It has the advantages over any one of the older methods of simplicity and accuracy. It has much wider possibilities for clinical investigative studies than do the other methods. In brief, the primary extraction is made with a mixture of glacial acetic acid and ethyl acetate, followed by successive extractions with hydrochloric acid, ether and again hydrochloric acid. Values are expressed in gamma per 100 cc. of erythrocytes, normal values ranging from 20 to 45. In disease, protoporphyrin may be elevated to 200 and even 430 gamma.[62]

Extraction of other organs and tissues usually depends on acetic acid-ether extracts of the ground tissues, purification being done by a series of extractions involving hydrochloric acid and ether. Neutralization of the hydrochloric acid solution with acetate, using Congo red as an indicator, drives the porphyrin back into the ether. Hydrochloric acid solutions of over 5 per cent always extract the porphyrin from the ether. The protoporphyrin in liver has been extracted in this manner by Fischer[89] and by Rimington.[11]

Summary

It may be said that protoporphyrin is intimately associated with certain of the pigments and enzymes concerned in oxidative processes. Iron and protoporphyrin have always been found in combination in physiologic conditions. Neither has been proved to have any important separate functional capacity. The protoporphyrin forms a convenient and suitable binding necessary to the iron.

Circumstantial evidence points to coproporphyrin 3 and uroporphyrin 3 as excretory products of protoporphyrin. Coproporphyrin 1 and uroporphyrin 1 cannot be breakdown products of protoporphyrin 9, the only protoporphyrin known in the body. If in the future a Type 1 porphyrin is found in a pigment or enzyme, uroporphyrin 1 and coproporphyrin 1 will be acceptable as its possible excretion products. In the meantime they must be considered as abortive side products of porphyrin synthesis.

Protoporphyrin is found free in red cells, and is associated with certain young cells called "fluorescytes" and with reticulocytes. In diseases in which these cells are numerous, the red-cell protoporphyrin increases and can be considered a supply for the building up of hemoglobin. Many recent advances have been made relating to qualitative and quantitative determinations. Clinical investigation of the protoporphyrin of blood in disease has been facilitated.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31011

PRESENTATION OF CASE

First admission. A fifty-five-year-old woman was admitted to the hospital with an impacted fracture of the neck of the right femur.

About twenty-four hours before admission the patient became dizzy and fell to the floor. An x-ray examination revealed an incomplete impacted fracture of the right femoral neck. Four years previously the patient had fallen at home and incurred a similar fracture of the left femoral neck, which was treated by traction with a good result. One and a half years prior to admission she had fallen on her left shoulder with a resultant impacted fracture of the surgical neck of the left humerus which also healed with a good result. At about that time she had had an attack of "nervous prostration" lasting six weeks, with frequent "dizzy" or "sinking" spells, which caused her to fall down. About two months before entry she had fallen and twisted her ankle. The patient was said to have had congenital syphilis; this was diagnosed at the age of three years and apparently was inadequately treated. Her teeth had been poor and were extracted at an early age. She had two adult children by her first husband; both were born after a full-term normal pregnancy and both had negative Hinton tests. She had been married to her second husband for two and a half years.

Physical examination on admission revealed a fairly well-developed and well-nourished woman incessantly picking at the bedclothes or rubbing her hands together; she was vague about her past history and unco-operative. There was spasm about the right hip and limitation of motion but no shortening.

The temperature was 99°F., the pulse 86, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,010,000, with 75 per cent hemoglobin, and a white-cell count of 6800. The urine varied in specific gravity from 1.002 to 1.014, with a 0 to a ++ test for albumin and a sediment containing few to many white cells and a few red cells. The blood protein, calcium, phosphorus and phosphatase levels were normal. Blood Hinton and Wassermann tests were positive.

Since the fracture was impacted and in good position, it was treated with balance suspension. The patient throughout her stay was unco-operative, suspicious and difficult to manage. A psychiatric examination showed her to be emotionally unstable — "irritable and belligerent, but not demented or psychotic"; there was no confusion or impairment of memory. At the end of six weeks the patient resisted efforts to get her up on crutches, and she was discharged against advice.

Second admission (four months later). Following her discharge the patient was able to get about a little, but her activity was limited by the frequent occurrence of "sinking" spells, during which she became weak and was forced to sit down for a time. Six hours before entry, her husband left her feeling quite well. Half an hour before entry he returned and found her in her chair, comatose and stiff.

Physical examination revealed a comatose woman breathing in gasps. The only response was slight withdrawal of the extremities from painful stimuli. All the extremities were spastic. The head and eyes were turned to the left. There were spontaneous, horizontal, nystagmoid movements. The pupils did not react to light. There was no papilledema. All the deep tendon reflexes were brisk, particularly on the left. There were bilateral extensor plantar responses, and a positive Hoffmann sign on the left.

A lumbar puncture revealed clear fluid under a pressure equivalent to 130 mm. of water and containing 6 lymphocytes and 15 red cells per cubic millimeter. The total protein was 234 mg. per 100 cc. The Wassermann test was positive. The gold-sol curve was 5555555500. The urine had a specific gravity of 1.022, with no albumin or sugar but with a ++ test for acetone and a rare granular cast in the sediment.

The temperature on admission was normal, but four hours later it spiked to 105°F. and during the next twenty-four hours it rose to 108°F. The pulse rose to 160 and the respirations to 50.

The white-cell count was 16,100, with 80 per cent neutrophils. A blood culture was negative. A roentgenogram of the chest taken at the onset revealed indefinite fine areas of increased density in the left lung field. X-ray examination of the skull was negative. Sulfadiazine was administered (1.0 gm. every six hours) by Levine tube, and food and fluid intake were maintained in the same fashion. A second lumbar puncture revealed a cell count of 29 lymphocytes, 7 neutrophils and 29 red cells.

After reaching 108°F. on the third hospital day, the temperature gradually fell toward normal. The patient remained comatose. Deviation of the head and eyes to the left occurred intermittently. At times there was skew deviation of the eyes. On one occasion the pupils were reported to react slightly to light. The extremities were sometimes spastic and

*On leave of absence.

sometimes flaccid. At times the tendon reflexes could not be obtained.

On the fourth hospital day, the temperature rose to 101°F., the lungs filled with coarse moist rales and the patient died.

Differential Diagnosis

Dr. Raymond Adams*: Let us scrutinize this record with the purpose in mind of selecting data that point to the site of the pathologic process, leaving the matter of etiology until later.

In the early part of the history the outstanding symptoms were attacks of dizziness and sinking spells. In such attacks the patient had fallen repeatedly and had suffered numerous injuries. The first problem that confronts us, then, is the nature of these spells. Were they attacks of giddiness such as occur so often in nervous, anxious individuals, or were they attacks of vertigo such as are often observed in diseases of the labyrinth, eighth nerve or vestibular nuclei? Were they straightforward syncopal attacks, brief seizures or apoplectic phenomena? I shall assume, for the reason that the patient repeatedly fell and injured herself, apparently having at the moment none of the usual protective reflexes against injury, that they were not giddy or vertiginous spells but either epileptiform or apoplectiform attacks. The description is inadequate to make a sharp distinction between these two.

The examination at the first hospital entry disclosed some interesting findings. The patient was picking at the bedclothes, rubbing her hands together, unable to relate the history of her illness, uncooperative and apparently lacking in insight. Further notes point out that she was suspicious and difficult to manage, being emotionally unstable and belligerent. Even though the psychiatric consultant reassures us that the patient was not "demented or psychotic," I do not recognize this as normal. Change in personality, lack of insight, confusion, emotional instability, irritability and suspiciousness are marks of intellectual deterioration due to a disorder of the brain. If acute, it may be on a toxic basis, but if chronic, as it was in this case, it is indicative of structural brain disease often termed an organic reaction type by psychiatrists. These signs, of course, have no specific localizing value but point to a diffuse involvement of the cerebrum.

The symptoms that precipitated the second admission were much more dramatic. Six hours before entry the patient had appeared quite well, and a few hours later she was found in coma. In addition, the extremities were stiff and rigid, the head and eyes deviated to the left, the eyes jerked from side to side, the pupils were unreactive, and the plantar responses were bilaterally extensor. It seems to me that the patient at that time was functioning at essentially a brain-stem level. The description of the position of the limbs is incomplete, but it is possible that she was assuming postures seen in decerebrate rigidity. The most we can conclude is that there was abrogation of all cerebral function.

There are two possible explanations of the spontaneous nystagmoid movements. There might have been a lesion in the vestibular nuclei or in the connections between these nuclei and the third, fourth and sixth nuclei by way of the medial longitudinal fasciculus. If these nystagmoid movements were always toward one side they might have been caused by a focus of irritation, that is, epilepsy, in the contralateral cerebral hemisphere. I shall assume that the former was the case.

The unreactive pupils are of little localizing value. They could have been Argyll–Robertson pupils or an iridoplegia due to damage of the third-nerve nuclei. Skew deviation was reported. This term applies to a lack of parallelism between the axes of the eyes so that one looks up and outward and the other is deviated down and inward. Skew deviation is usually associated with external ophthalmoplegias but occasionally with lesions of the cerebellum. The best interpretation here is that there was a disorganization of ocular movement at the level of the pons or midbrain.

Slight deviation of the head and eyes to the left requires a word of explanation. Stimulation of the adversive field of Brodmann's† Area 8 of the cerebral cortex causes turning of the head and eyes to the opposite side, and an epileptic focus does the same. Destructive lesions of these areas cause paralysis of contralateral gaze. Also destructive lesions just lateral to sixth nerve nucleus cause paralysis of gaze toward the side of the lesion, and usually a unilateral sixth-nerve palsy as well. I shall assume in this case that the head and eyes were turned to the left because of a disturbance in function at the level of the pons. The nystagmoid movements are an expression of the same disturbance. Here I am treading on dangerous ground, because they might have been due either to a pontine or a midbrain lesion or to a focus of irritation, that is, epilepsy, in the right frontal lobe.

The patient never actually moved her arms and legs except once when they were pricked with a pin. Was there paralysis for voluntary movement? One cannot say because she was comatose. Reflex withdrawal from a painful stimulus may be a spinal-reflex withdrawal and so does not give much assistance. Also, intermittent stiffening of the limbs could have been due to a transient release of postural mechanisms in the lower brain stem. Bilateral Babinski signs in a comatose person may only signify that the motor cortex is disordered as badly as the rest of the brain. I am unable to assume from all this that there was a quadriplegia due to a brain-

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†Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* 334 pp. Leipzig: J. A. Barth, 1909.

stem lesion, although functionally there undoubtedly was a quadriplegia.

Deep coma lasting four days is always proof of severe brain disease. It can be due to the occlusion of the basilar or one of the other large cerebral arteries, to brain hemorrhage, to any of several metabolic diseases in which insufficient oxygen or glucose is sent to the brain or to repeated convulsions. Again, when interpreted physiologically, it is indicative of either a widespread and severe cerebral disorder or a disease in the vicinity of the thalamus and midbrain.

The temperature of 108°F., the pulse of 160 and the respirations of 50 are of interest. Often in midbrain and pontine lesions the temperature, pulse and respirations rise to great heights, possibly owing to a dysfunction of the heat-dissipating mechanism. Such could be the mechanism here. In comatose patients, however, pulmonary congestion and edema and bronchopneumonia are so frequent that these must always be given first consideration. With a leukocytosis and the x-ray films of the chest showing fine areas of increased density in the left lung field, bronchopneumonia is the likeliest explanation. In comatose patients the ground is always prepared for pulmonary infection, because of the disturbance of pulmonary vasomotor reflexes.

From this part of the discussion I come to the conclusion that we are dealing with a disease that diffusely involved the cerebrum and that the attacks of dizziness were either epileptic convulsions or minor apoplexy. Furthermore, in the last four days of life, there was an almost complete suppression of cerebral function due either to status epilepticus or to a lesion of the midbrain and pons.

Now let us search for the etiologic factor. The blood Hinton and Wassermann and the cerebrospinal-fluid Wassermann tests were positive. The spinal fluid showed increased cells, increased total protein and a first-zone colloidal gold reaction. This is the usual picture of general paresis, but it is not pathognomonic as was once believed. I have seen similar cerebrospinal-fluid findings in asymptomatic and other forms of neurosyphilis. The patient was said to have had congenital syphilis — a statement without proof. I do not believe that a congenital syphilitic patient would live until fifty-five before having symptoms. I know of no older patient than one who developed general paresis at twenty-nine. It is probable that this woman acquired syphilis in adult life, possibly after the birth of her children.

Of course, paretic neurosyphilis could have accounted for the whole picture. It is the obvious explanation of the personality changes, the curious dizzy spells and the nervous prostration. That paretic patients sustain injuries in such spells is well known, and old untreated patients often have subdural hematomas for this reason. These hematomas, now rarely seen, were once thought to be syphilitic. But what about the final episode? On the basis of neurosyphilis there are two possible explanations: convulsions, since 50 to 60 per cent of paretics have them, and syphilitic basilar arteritis, with thrombosis and infarction. Although tempted at first to conclude that this patient merely went into coma and died of status epilepticus, I am compelled, because of the skew deviation, to assume a vascular lesion of the pons, namely, a thrombosis of the basilar artery with infarction of pons and midbrain. If the eyes were merely roving independently, as they often do in a comatose person, then this diagnosis is probably wrong.

Clinical Diagnoses

Cerebral hemorrhage.
Central-nervous-system syphilis.

Dr. Adams's Diagnoses

Thrombosis of basilar artery, with infarction of pons.
General paresis.
Bronchopneumonia.

Anatomical Diagnoses

General paresis.
Bronchopneumonia.

Pathological Discussion

Dr. Charles S. Kubik: Dr. Adams gave excellent reasons for thinking that this patient had thrombosis of the basilar artery. None was found, however, nor was there occlusion of any of the other main arteries. There was general paresis, with marked involvement of the cerebral cortex. There was also bronchopneumonia.

There was cloudiness of the arachnoid membrane. The convolutions were atrophied only slightly, and there was little enlargement of the lateral ventricles. Microscopically, the subarachnoid space and the perivascular spaces of the small cortical blood vessels were infiltrated with lymphocytes and plasma cells. In the cortex many nerve cells were degenerated; there were numerous rod-shaped microglial cells, and a proliferation of astrocytes. The capillaries and arterioles were prominent and appeared to be increased in number. There was a granular ependymitis of the fourth ventricle.

The findings were characteristic of general paresis. It is interesting that there was little generalized cerebral atrophy.

CASE 31012

Presentation of Case

A forty-five-year-old woman was admitted to the hospital in coma.

Eight days prior to admission the patient complained of a headache, which became so severe the

following morning that she was forced to lie down. Shortly afterward she was found unconscious. The left side was completely paralyzed, there were slight twitchings of the right arm and leg, and the tongue was bleeding from an area where a small piece had been bitten out. The patient remained unresponsive until admission, except for two or three occasions when she said a few words and appeared to understand what was being said to her. The systolic blood pressure when she was found was said to have been 220; it varied between 140 and 180 afterward. The diastolic pressure was unknown, and there was no knowledge of previous hypertension.

The patient had had an "inflamed ovary" removed and an appendectomy nine and three years prior to admission, respectively. She had always bruised easily.

Physical examination revealed an unconscious woman, occasionally moaning and moving the arm and leg on the right but not on the left. There was a "mousey" odor to the breath. The skin and scleras had an icteric tinge. Numerous bruises, petechial hemorrhage and dilated capillaries were present over the extremities and to a lesser extent on the extremities, face, chest and back. The neck was stiff. The heart was slightly enlarged to the left, but there were no murmurs. A mass was palpable in the upper half of the epigastrium, rather more to the left than to the right of the midline. The pupils were of average size and equal and reacted slightly to light. The eyelids were closed, and the eyes were directed straight forward. The fundi were negative except for somewhat tortuous retinal arteries and a certain amount of arteriovenous nicking. The tendon reflexes were active and equal. There were extensor plantar responses bilaterally.

The temperature was 101°F., the pulse 76, and the respirations 16. The blood pressure was 160 systolic, 85 diastolic.

Examination of the blood revealed a red-cell count of 4,090,000, with 12.8 gm. of hemoglobin, and a white-cell count of 9600, with 75 per cent neutrophils, 10 per cent lymphocytes, 14 per cent monocytes and 1 per cent basophils. There was considerable polychromasia, platelets were present in fairly good numbers, and there were no toxic changes in the neutrophils. The clotting time was prolonged. Clot retraction was normal. The urine had a specific gravity of 1.026, with a ++ test for albumin and a sediment containing many red and white cells and occasional clumps of pus. The prothrombin time was 35 seconds (normal, 16 seconds). The blood sugar was 100 mg. per 100 cc., the serum nonprotein nitrogen 37 mg., and the van den Bergh 2.7 mg. direct, and 4.85 mg. indirect.

A roentgenogram of the chest revealed a generalized increase in the vascular markings. Examination of the abdomen showed an area of calcification in the left side of the pelvis that was thought to be a calcified fibroid and a calcified node in the right lower quadrant. Examination of the skull was unsatisfactory because of the patient's condition.

A lumbar puncture on admission revealed grossly bloody and xanthochromic fluid under an initial pressure equivalent to 300 mm. of water. Its cell count was 10,200 red cells and 598 white cells, of which 513 were neutrophils. The protein was 264 mg. per 100 cc. One week later a second tap revealed clear yellow fluid with a total protein of 153 mg. per 100 cc.; no cell count was done. The spinal-fluid Wassermann test was negative.

The patient became progressively less responsive; the temperature fell to normal, and the pulse rate varied between 70 and 105. She was given 25 per cent, and later 10 per cent, dextrose in water intravenously, together with normal saline solution and vitamins. Four milligrams of Hykinone was administered daily. On the eleventh hospital day the patient began having generalized convulsive seizures, each lasting five to ten minutes. After two or three days, the seizures became milder and the patient began to improve. She became more responsive and began to talk a little. It was thought that a left homonymous hemianopsia could be demonstrated. The mental status continued to improve. On the thirty-fifth hospital day there was some voluntary motion of the left foot and hand. By this time the prothrombin time had gradually fallen to 28 seconds (normal, 20 seconds) and the van den Bergh was 0.6 mg. direct, and 0.9 indirect.

On the thirty-seventh hospital day the patient suddenly had a chill, followed by a rise in temperature to 102.6°F. There was considerable right costovertebral-angle tenderness. The urine sediment contained innumerable red and a few white cells, and a culture was positive for colon bacilli. A blood culture was also positive for colon bacilli. The neck again became stiff, and the patient lost consciousness. The white-cell count rose to 27,700, with 85 per cent neutrophils. Death occurred on the forty-sixth hospital day.

Differential Diagnosis

Dr. Jacob Lerman: Were the urine examinations done on catheter specimens?

Dr. Wyman Richardson: They included at least one catheter specimen.

Dr. Lerman: I should like to comment on some of the highlights of the clinical findings. Apparently coma occurred a day or so after she became ill and after she developed headache. She had obvious left-sided paralysis, which points to a lesion on the right side of the cerebrum, but she had twitchings on the right, suggesting a more generalized involvement. She had convulsions at home and also while in the hospital. Those in the hospital were general in nature, not limited to one side. Unfortunately, nothing definite can be said about the presence or absence of hypertension. The reading before she came into the hospital suggests hypertension, but

those in the hospital do not. The changes in blood pressure may have been due to changes in spinal-fluid pressure.

There is a note saying that the patient bruised easily, but that really means nothing unless confirmed by physical findings or laboratory data. Many people give such a history, and it is not significant.

On physical examination certain findings, including a "mousey" odor to the breath, suggest liver disease. One can also observe the same odor in patients with severe infection, particularly those with septicemia. She certainly had jaundice and an enlarged organ, which I take to be the liver, primarily because of its location and also because of the presence of jaundice and a moderately elevated van den Bergh reaction. Apparently the left lobe of the liver was enlarged, since the mass was to the left of the midline. Left-lobe enlargement of the liver suggests syphilis. No mention is made of the blood Hinton test, and there is no evidence of syphilis elsewhere, the spinal-fluid Wassermann test being negative. Consequently, syphilis need not be considered.

She had bruises, petechial hemorrhages and dilated capillaries, which may be manifestations of a hemorrhagic disease, such as thrombocytopenic purpura or symptomatic purpura, or of septicemia, such as blood-stream infection with the meningococcus. In the presence of liver disease confirmed by a prolonged prothrombin time, however, one can adequately explain these signs.

The tendon reflexes were active and equal. That is strange because from the description one would expect inequality. The right arm moved; the left arm did not. Bilateral extensor plantar reflexes also indicated generalized injury to the brain rather than localized injury, which we assumed from the description of the patient. Is it possible that she had not yet developed complete evidence of a unilateral cerebral hemorrhage? Seven days had passed, and one would expect complete manifestation of the injury by that time. Since she did have positive Babinski signs, then the evidence of injury was complete. It is hard to reconcile the various reflex changes with a unilateral cerebral lesion. One may assume generalized injury to the brain, such as could be produced by diffuse hemorrhage, or, in addition to a right cerebral lesion, a previous injury to the left cortex, about which we know nothing.

She had slight anemia and polychromasia, the latter indicating excessive stimulation of bone marrow. The number of platelets was normal, which rules out idiopathic thrombocytopenic purpura. The elevated prothrombin time and van den Bergh values fit in with other evidence of liver disease. The urinary findings indicate pyelonephritis or possibly diffuse hemorrhage involving the kidney substance.

DR. RICHARDSON: I ought to give you additional information. The patient had to be on constant drainage.

DR. LERMAN: Then the urinary findings are not of much value, and I shall have to disregard them.

The lumbar puncture yielded a spinal fluid containing a lot of blood, including old blood, as evidenced by the xanthochromic fluid; the white-cell count was high, consistent with irritation produced by the bleeding, and the Wassermann test was negative. There is no mention of organisms; presumably none were found.

The patient lost ground for a while and then improved. The left homonymous hemianopsia points to a lesion posterior to the chiasm on the right side in the optic radiations going to the occipital lobe. This is consistent with the left-sided paralysis that the patient had.

She then had generalized convulsions, some temporary improvement in the prothrombin time and the van den Bergh reaction and, finally, a colon-bacillus septicemia.

It is difficult for me to put all these findings together. Certainly one can rule out thrombocytopenic purpura as the etiologic factor. Could she have had symptomatic purpura as a result of infection? There is not enough evidence in the early part of the history to indicate a general infection. The problem is to explain the development of coma, which was undoubtedly due to extensive cerebral hemorrhage, including subarachnoid hemorrhage, in addition to at least one major lesion on the right side to account for the left-sided paralysis and the left homonymous hemianopsia. One can arrive at this syndrome by various routes.

First, she may have developed jaundice from acute hepatitis, toxic or infectious in nature, which resulted in an elevated prothrombin time and a tendency to diffuse hemorrhage in the skin and brain. Since the process was rather acute and fulminating, the liver damage may have been in the nature of acute or subacute yellow atrophy. The colon-bacillus infection must then be considered as a terminal event, perhaps due to the inlying catheter, or to a long-standing pyelonephritis that merely spread terminally.

Second, the patient may have had a serious infection with septicemia, type unknown. It might have been a colon-bacillus infection that was not recognized at first. The septicemia produced jaundice and the hemorrhagic tendency. A possible subheading under this mechanism is that the absorption of hemolyzed blood from the sites of hemorrhage caused plugging of bile capillaries sufficient to produce jaundice. In either case, the jaundice did not play any role of importance. Death was due to recrudescence of the original infection.

Third, the patient may have had bacterial endocarditis due not to *Streptococcus viridans* but to the

colon bacillus. Such an infection would explain many of the central-nervous-system findings and even the jaundice. On the other hand, there is no history of pain, which is so frequently associated with the embolic phenomena of bacterial endocarditis, unless, of course, cerebral embolism occurred first and knocked out all conscious sensations There are no findings in the heart to point to endocarditis. The absence of any information regarding blood cultures until the final culture was obtained steers one away from a diagnosis of endocarditis.

One must also think of such rare conditions as hepatoma, with cerebral manifestations resulting from metastatic involvement of the cerebrum. This would not explain, however, the tendency to skin hemorrhages, unless there was an associated cirrhosis. Rupture of an aneurysm on the right side of the brain could explain all the cerebral findings but not the peripheral findings, such as the tendency to hemorrhage in the skin, and the liver damage.

Thus I am right back to my first thought; namely, this was a patient with jaundice due to acute hepatitis, probably subacute yellow atrophy. The hemorrhagic tendency resulting therefrom then produced cerebral vascular bleeding, diffuse throughout the brain and subarachnoid space, but including one major lesion on the right side. In addition one might suppose that the colon bacilli would localize in the spinal fluid, and also in the areas of cerebral damage.

Dr. Richardson: I want to give Dr. Lerman more bits of evidence. In the first place, the capillary dilatation was not diffuse, but true spider-angioma telangiectasis. This was more striking than in any patient I have ever seen — small central red spots with lines radiating in a characteristic spider design, most marked over the chest and abdomen but also present on the arms and elsewhere. I did not tumble to this the first night I saw the patient, but the next morning it seemed important. At that time I also noticed jaundice and the mousey odor to the breath. I thought it was all due to hepatic failure, and in the note I wrote, I said that she had primary liver failure with a bleeding tendency, causing some type of bleeding lesion in the brain. Later I discovered that for many years she had had a high alcoholic intake; in fact, one of the surgeons who had operated on her previously reported that she had had at that time a cirrhosis of the liver. My thought was that she had cirrhosis of the liver with superimposed acute hepatitis and cerebral hemorrhage. I thought the latter was subarachnoid and possibly due to a congenital aneurysm, with more bleeding than normally would have been expected. I did not see the patient at the very end, but I believe that the second episode meant that she had another hemorrhage.

A Physician: What about the mass in the epigastrium?

Dr. Richardson: I thought that it was the liver, but not entirely the left lobe.

Dr. Lerman: I did not mean to indicate that the mass was entirely due to left-lobe enlargement, but certainly a prominent left lobe points toward syphilis. The additional history indicates extensive chronic liver disease rather than an acute episode of liver disease, and confirms my supposition that the hemorrhagic tendency was due to liver disease. Another possibility, which I think I can dismiss, is the development of a hepatoma in a cirrhotic liver. She could have had a hepatoma with metastases to the brain, and coma could have been produced by hemorrhage into one or more metastases.

Dr. Joseph C. Aub: Hepatoma rarely metastasizes to the brain. There are a few cases in the literature, but they are unusual.

Dr. Lerman: I thought that a hepatoma metastasized to almost any organ.

Dr. Aub: Sometimes to lung, and sometimes brain; but it is rare.

Dr. Lerman: I admit that it is unusual, but I was trying to find one diagnosis to cover all the findings. I shall have to stick to my original diagnosis of hemorrhagic tendency from liver disease.

Dr. Richardson: We considered hepatoma in the beginning on the basis of the mass and also because of the polychromasia, but I finally explained the latter in the way Dr. Lerman did, that is, as due to hemorrhage, and discarded the idea of hepatoma.

Clinical Diagnoses

Cerebral hemorrhage.
Alcoholic cirrhosis of liver.
Acute hepatitis.
Septicemia (colon bacillus).

Dr. Lerman's Diagnoses

Cerebral hemorrhage, diffuse and right cerebral.
Subarachnoid hemorrhage.
Portal cirrhosis.
Acute hepatitis.
Septicemia (colon bacillus).
Pyelonephritis?

Anatomical Diagnoses

Cerebral hemorrhage, old: right temporal lobe.
Cerebellar hemorrhage, recent.
Cerebral infarction, right frontal and parietal, old.
Toxic cirrhosis of liver.
Septicemia (colon bacillus).
Acute pyelonephritis.
Bronchopneumonia, with abscess formation.
Petechiae of skin, gastrointestinal tract, pleura, epicardium and endocardium.
Jaundice.
Operations: appendectomy and right oöphorectomy, old.

Pathological Discussion

Dr. Benjamin Castleman: Before Dr. Kubik tells us what was found in the brain, I shall say

that there was cirrhosis of the liver. It did not look like the ordinary alcoholic type. The nodules varied in size tremendously. The usual case of alcoholic cirrhosis shows uniformly small nodules. These suggested the healed atrophy or toxic type of cirrhosis. We found no evidence of acute hepatitis.

DR. RICHARDSON: She had, however, been in the hospital a long time.

DR. LERMAN: Forty-six days.

DR. CASTLEMAN: She had, as you know, a colon-bacillus septicemia and numerous abscesses to the kidney. I do not know whether the abscesses developed after her admission to the hospital, but she probably had some degree of pyelonephritis before she came in. The lungs were diffusely studded with areas of bronchopneumonia that had broken down and formed abscesses. She had a great deal of infection, which may have accounted in part for the jaundice; that is, the jaundice may have been due to the combination of overwhelming infection and a poorly functioning liver. I do not believe that the liver disease itself was responsible for that amount of jaundice.

DR. RICHARDSON: If you had seen her when she came in, it might have altered your opinion. The liver was acutely involved. She was given tremendous amounts of glucose intravenously.

DR. CASTLEMAN: Did the liver shrink?

DR. RICHARDSON: I cannot remember. I do not see any note to that effect but believe that it did. She began to improve and everyone felt encouraged, and then she had a sudden episode and went down hill.

DR. CHARLES S. KUBIK: Most subarachnoid hemorrhages, as you all know, are due to ruptured aneurysms. We did not find any aneurysm in this case. There was an area of infarction in the right frontal lobe. This probably contributed only slightly to the symptomatology. The main lesion was an old hemorrhage in the right temporal lobe. This hemorrhage, measuring 8 cm. in length, extended practically the whole length of the temporal lobe. It was surrounded by a firm connective-tissue capsule about 0.5 mm. in thickness. There was also a recent hemorrhage in the cerebellum, which unquestionably accounted for the episode that occurred shortly before the patient died and was probably the chief cause of death. It had broken through into the subarachnoid space. There was but little arteriosclerosis. I am not sure whether the older hemorrhage had leaked into the ventricle or into the subarachnoid space, or into both.

DR. CASTLEMAN: Do you think that this was the usual form of cerebral hemorrhage? May it not have been due to jaundice?

DR. KUBIK: I do not know. I have seen three cases with severe jaundice and cerebral or subarachnoid hemorrhage. The two with cerebral hemorrhages came to autopsy; the one who had a subarachnoid hemorrhage is still living.

DR. CASTLEMAN: This patient's heart weighed about 400 gm., which is not particularly large. Do you think that she had had hypertension in the past?

DR. RICHARDSON: When the story was given to me I was inclined to doubt it.

DR. CASTLEMAN: If we knew that she had not had hypertension, we could blame the hemorrhage on the jaundice.

DR. RICHARDSON: There was just the one reading, taken shortly before she entered the hospital. At the time of one of her previous operations there was no hypertension.

DR. KUBIK: The systolic reading of 220 was obtained after onset of the first hemorrhage, and the elevation might have resulted from increased intracranial pressure.

DR. RICHARDSON: I have had personal experience with three patients with severe liver damage accompanied by severe cerebral bleeding of one sort or another. One had a subdural hematoma that was successfully operated on; the hemorrhage may have been due to trauma, although the amount of bleeding was more than one would expect. At this moment there is a patient in the hospital with severe alcoholic cirrhosis who has probably had some cerebral bleeding. My interpretation is that the bleeding is due to prothrombin lack, although there must be something to precipitate the bleeding.

DR. CASTLEMAN: Is it not also true that a person with as large a cerebral hemorrhage as this would usually have died before there was a chance for a second episode.

DR. KUBIK: Yes; massive cerebral hemorrhages are practically always rapidly fatal, the patient rarely surviving more than a few days.

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NAVAL MEDICAL OFFICERS

Although the Army of the United States has indicated that its need for medical officers is, for the moment, covered by recent graduates from medical schools who have completed their internships and residencies, an urgent demand for such officers in the United States Navy, whose personnel and activities are constantly increasing, still continues. As noted in a letter published elsewhere in this issue of the *Journal*, the physical requirements for the Navy Medical Corps have been lowered, the age limit has been increased and waivers may be obtained for certain disqualifying physical defects. Undoubtedly the applications of many physicians were refused because of one of these reasons. Each one of these men, as well as others who believe that their contributions to the war effort would be greater in a service capacity than in civilian practice, should respond to this appeal.

A SURGEON ON WAR AND PEACE

Colonel Elliott C. Cutler, chief consultant in surgery, Army of the United States, European Theater of Operation, and Moseley Professor of Surgery, Harvard Medical School, delivered on May 6, 1944, at St. John's College, Cambridge, England, the Linacre Lecture on the subject "A Surgeon Looks At Two Wars." Colonel Cutler's lecture, in abridged form, has appeared as the leading article in the September 30 issue of the *Lancet*.

The comparison between the types of injuries sustained in this war and their treatment and those of twenty-five years ago is interesting; more important is the apparently considerable increase in psychiatric casualties over those of 1916–1918 despite a more rigid screening at the source, and the theories advanced to explain this experience. Chief among these explanations rank an easier discipline in our army of today, leaving an avenue of escape open for the battle-weary soldier, inferior leadership by subaltern officers, and a loss of self-sufficiency and independence in a country where overpaternalism has softened the population.

In particular, Colonel Cutler emphasizes the military value of hate in carrying a war through to its successful conclusion; he points out that it is a military fault of the English and Americans that they are naturally peace-loving and have as yet found little cause for holding such a personal grudge against the Germans as have the Russians. This hatred we have had cause to develop against the Japanese, and the Japs we are able to hunt down with relentless fury, for their atrocities have been committed against ourselves.

Future opportunities for Germany to fling herself at the throats of civilized mankind must be denied, and Colonel Cutler closes his lecture on the note that those who make the peace must this time be those who have been to war and know what it

means. It is expressly stated that war must be waged in hate, and it is implied that hate must not be forgotten when the peace is made.

In the same issue of the *Lancet* is one of the sanest and most temperate editorials that it has been our fortune to read — an editorial that bespeaks the innate fair-mindedness of the British nation. We are reminded that this war is not between men and a different species, but between men and men, in whom all the human elements are mixed. True, our adversaries have been led into intolerable deeds by their psychologic immaturity, but "five years have not changed our opinion that a peace of understanding has more permanence than a peace of passion."

"The young men who now command our thoughts and bear our hopes," the editorial continues, "are often heroes but seldom fanatics; and for our part we should say that one of their greatest achievements has been to combine military resolution with an objective attitude toward the enemy."

An attempted destruction of Germany will sow the seeds of hate and prepare for a future harvest of calamity. Our only hope is in a modeling of civilization, to help young Germans "feel it an adequate purpose in life to rebuild out of the ruins the Germany of Kant and Goethe and Beethoven — to whom we might add Virchow, Koch and Ehrlich, or others according to taste."

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ALLEN — Gardner W. Allen, M.D., of Boston, died July 12. He was in his eighty-ninth year.

Dr. Allen received his degree from Harvard Medical School in 1882. He was formerly professor of genitourinary surgery at Tufts College Medical School, and surgeon in the Genitourinary Department of the Boston Dispensary. He was a member of the American Association of Genito-Urinary Surgeons, Massachusetts Historical Society, American Antiquarian Society, Naval Historical Foundation, American Historical Association and the Military Historical Society of Massachusetts.

DAWSON — Raymond J. Dawson, M.D., of Methuen, died November 20. He was in his thirty-ninth year.

Dr. Dawson received his degree from McGill University Faculty of Medicine, Montreal, in 1932. He interned at the Lynn Hospital and Montreal General Hospital, and had practiced in Methuen from 1934 until entering the Army of the United States as a lieutenant in the Medical Corps, from which he was eventually honorably discharged. He was a fellow of the American Medical Association.

His widow, his parents and three brothers survive.

HAWES — Edward E. Hawes, M.D., of Hyannis, died November 30. He was in his eighty-third year.

Dr. Hawes received his degree from the University of Vermont College of Medicine in 1886. He was on the staff of the Cape Cod Hospital.

OSSEN — Emil Z. Ossen, M.D., of Quincy, died December 16. He was in his thirty-ninth year.

Dr. Ossen received his degree from State University of Iowa College of Medicine, Iowa City, in 1931. He was staff physician of the Norfolk County Hospital from 1932 to 1937. He was visiting physician at the Beth Israel Hospital and on the staff of the Quincy City Hospital and the Milton Hospital. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

SANBORN — Byron Sanborn, M.D., of Topsfield, died December 20. He was in his seventy-first year.

Dr. Sanborn received his degree from Dartmouth Medical School, Hanover, New Hampshire, in 1900. He served as associate medical examiner for one district of Essex County from 1930 to 1939. He had also served as examining physician for Topsfield public schools and was town medical adviser. He was a fellow of the American Medical Association.

His widow and a son survive.

YOUNG — Evangeline W. Young, M.D., of Framingham, died December 20. She was in her seventy-first year.

Dr. Young received her degree from Tufts College Medical School in 1906. She practiced medicine in Boston until 1934. She was a former member of the Massachusetts Medical Society.

A brother survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1944

RÉSUMÉ

Diseases	November 1944	November 1943	Seven-Year Median
Anterior poliomyelitis	35	24	6
Chancroid	2	*	*
Chicken pox	1024	1281	973
Diphtheria	28	29	14
Dog bite	590	592	598
Dysentery, bacillary	24	22	30
German measles	54	66	39
Gonorrhea	445	510	421
Granuloma inguinale	1	*	*
Lymphogranuloma venereum	2	*	*
Malaria	50	25	1
Measles	355	816	816
Meningitis, meningococcal	31	37	8
Meningitis, Pfeiffer-bacillus	3	6	1
Meningitis, pneumococcal	3	4	†
Meningitis, staphylococcal	0	0	†
Meningitis, streptococcal	0	0	†
Meningitis, other forms	4	0	†
Meningitis, undetermined	2	11	†
Mumps	916	399	389
Pneumonia, lobar	162	225	234
Salmonella infections	4	7	6
Scarlet fever	777	704	594
Syphilis	420	617	503
Tuberculosis, pulmonary	222	215	220
Tuberculosis, other forms	11	18	20
Typhoid fever	1	3	3
Undulant fever	5	6	5
Whooping cough	499	405	557

*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

COMMENT

Poliomyelitis during November showed the expected marked drop in number of cases, there being only a little more than a third of the previous month's cases. Diphtheria, although at a comparatively low point as compared with the levels ten or fifteen years ago, was nonetheless twice the seven-year median for November. There is still plenty of need for stressing immunization.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Arlington, 2; Ashfield, 1; Boston, 5; Brockton, 1; Colrain, 1; Conway, 1; Dalton, 1; Easton, 2; Fort Devens, 1; Groveland, 2; Haverhill, 1; Holyoke, 1; Lexington, 2; Marlboro, 1; Melrose, 1; Middleboro, 2; New Bedford, 1; Pittsfield, 7; Rockland, 1; Williamstown, 1; total, 35.

Diphtheria was reported from: Ayer, 1; Boston, 2; Danvers, 1; Foxboro, 1; Framingham, 1; New Bedford, 3; Peabody, 2; Somerville, 13; Whitman, 1; Worcester, 3; total, 28.

Dysentery, bacillary, was reported from: Beverly, 2; Boston, 5; Dedham, 1; Everett, 1; Fall River, 4; Lawrence, 1; Lynn, 1; North Andover, 3; Somerville, 1; Stoneham, 1; Winchester, 2; Worcester, 2; total, 24.

Encephalitis, infectious, was reported from: Newton, 2; Quincy, 1; total, 3.

Malaria was reported from: Boston, 2; Camp Edwards, 8; Fort Devens, 16; Cushing General Hospital, 16; Haverhill, 4; Hingham, 1; Woburn, 1; West Bridgewater, 1; Worcester, 1; total, 50.

Meningitis, meningococcal, was reported from: Arlington, 1; Boston, 9; Cambridge, 2; Canton, 1; Chelsea Naval Hospital, 1; Easton, 1; Everett, 1; Falmouth, 1; Framingham, 1; Hardwick, 1; Lowell, 2; Lynn, 1; Medford, 1; Newton, 2; Palmer, 1; Quincy, 2; Watertown, 1; Webster, 1; Weymouth, 1; total, 31.

Meningitis, Pfeiffer-bacillus, was reported from: Lawrence, 1; Springfield, 1; Wellesley, 1; total, 3.

Meningitis, pneumococcal, was reported from: Boston, 1; Cambridge, 1; Springfield, 1; total, 3.

Meningitis, other forms, was reported from: Boston, 2; Milford, 1; Needham, 1; total, 4.

Meningitis, undetermined, was reported from: Auburn, 1; Worcester, 1; total, 2.

Salmonella infections were reported from: Framingham, 1; Medford, 1; Salem, 1; Wellesley, 1; total, 4.

Septic sore throat was reported from: Boston, 10; Holyoke, 2; Marion, 1; Newton, 1; total, 14.

Tetanus was reported from: Beverly, 1; North Attleboro, 1; Quincy, 1; total, 3.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Rehoboth, 1; total, 1.

Undulant fever was reported from: Bridgewater, 1; Lawrence, 1; Mansfield, 1; Somerville, 1; Southbridge, 1; total, 5.

MISCELLANY

NOTE

The following physicians were accepted into fellowship in the American College of Surgeons during 1944:

Massachusetts: *Boston* — E. L. Carey, P. W. Hugenberger, A. C. Kallan, H. G. Lee, R. E. Mabrey, D. O. McKee, J. J. Michelsen and L. H. Nason; *Brookline* — J. F. Conway, C. J. Duncan and H. C. Rosen; *Brockton* — S. F. Peterson; *Cambridge* — R. W. Smith; *Fall River* — D. F. Gallery; *Norwell* — Ralph Heifetz; *Norwood* — D. J. Collins; *Salem* — F. P. Morse, Jr.; *Walpole* — G. O. Garcelon; *Westfield* — D. R. Hayes and J. J. Tomasi; *Worcester* — E. E. Fipphen, E. J. Medden and Adolph Meltzer.

New Hampshire: *Epping* — W. C. Montgomery; *Manchester* — D. J. Sullivan and S. W. Yudicky; *Nashua* — Philip McQuesten.

CORRESPONDENCE

NEED FOR NAVAL MEDICAL OFFICERS

To the Editor: The daily casualty reports emphasize the urgent need for medical officers, and the procurement of doctors for the United States Naval Reserve remains a number one priority at this time. A concentrated effort is being made to obtain approximately 3000 physicians in order to increase the efficiency of the present medical forces.

Doctors on the home front are sacrificing many peacetime pursuits in professional and social fields in order to preserve existing medical standards. It is evident, however, that a disproportion of medical personnel exists in many communities throughout the country. In some areas, the number of physicians exceeds the demands, whereas in others there is a definite shortage. The problem is largely one of redistribution. Each doctor should reach a conscientious decision whether or not he can make a greater contribution in a direct military capacity.

Physical requirements for the Navy Medical Corps have been modified considerably since the beginning of the war. Doctors may now be accepted up to the age of sixty. Those in the older age groups are assigned to naval hospitals, dispensaries, the Veterans' Administration and other naval activities ashore. Organic physical defects continue to be disqualifying, but waivers can be granted for a variety of conditions that were formerly unacceptable.

Without making any definite commitment, applicants may be interviewed at this office without prior appointment on any weekday. Additional pertinent information will be furnished, and individual problems can be discussed.

H. S. Glidden, Commander (MC), U.S.N.R.
Senior Medical Officer
Office of Naval Officer Procurement
150 Causeway Street
Boston 14

THE MACHINE AGE

To the Editor: Something grim has happened to society since the opening of the industrial revolution about one hundred and seventy years ago. Much of it should be the concern of the medical sciences.

For several generations there has been abroad in the world the notion that character, culture and contentment can come through the multiplication of machines. This illusion has had a large part in developing the emotions and social unrest which now finds us fighting a second world war.

When the excessive mechanization of society creates such fantastic and swiftly changing environments that distortion and deterioration of standards and values result, man's limited biologic equipment (including his mental, moral and spiritual potentialities) is unequal to the task of making normal peaceful adjustments.

Is this the law of diminishing cultural returns?

What, if anything, can the medical profession do to interpret and correct this pathology?

A. E. P. Rockwell, M.D.
241 Grafton Street
Shrewsbury, Massachusetts

BOOK REVIEWS

Tuberculosis of the Ear, Nose and Throat. By Mervin C. Myerson, M.D. 8°, cloth, 291 pp., with 88 illustrations. Springfield, Illinois: Charles C Thomas, 1944. $5.50.

Dr. Myerson has had an unusual opportunity to study tuberculosis of the upper respiratory passages at the Sea View and Metropolitan hospitals in New York City. In this book, he draws on his vast experience with more than 10,000 cases for the many salient facts that are presented.

Inasmuch as tuberculosis of the larynx is the lesion most frequently encountered in practice, over half the book is devoted to this disease. Treatment is covered in detail, and the reviewer is in full accord with the methods that are considered beneficial and those that should be discarded. Other chapters briefly consider tuberculosis of the nose, ear, oral cavity, tongue, pharynx and esophagus. Finally, he gives full consideration to tuberculosis of the trachea and bronchi. Recent concepts of tuberculosis of the bronchi, including etiology, diagnosis and pathology, are fully discussed, although its treatment still awaits further study and experience. The illustrations and drawings are excellent and help considerably in visualizing the pathology.

The author is outspoken in his opinions, which, on the whole, are based on sound scientific principles. This book will be invaluable to otolaryngologists, as well as to all men interested in the problem of tuberculosis.

Intravenous Anesthesia. By R. Charles Adams, M.D., C.M., M.S. (Anes.). 8°, cloth, 663 pp., with 75 illustrations. New York City: Paul B. Hoeber, Incorporated, 1944. $12.00.

With the ever-widening fields of usefulness of intravenous anesthetics, this book is most timely. Dr. Adams is to be congratulated on the comprehensive manner with which he

has treated this subject. The book should be read by every anesthesiologist, and it will make a useful addition to any surgical library.

The chapters dealing with the history of intravenous apparatus, methods and agents are excellent, being particularly valuable to those interested in the history of medicine. The fact that the historical aspects of intravenous methods are so well covered does not mean that the practical side of the subject has been neglected. About two thirds of the book are devoted to the barbituric acid derivatives, this being the group of drugs that has proved the most practical for intravenous anesthesia.

The chapter on the technic of intravenous injection is especially to be recommended. It contains many suggestions that will prove helpful to anyone who is called on to do venipuncture, whether or not for the administration of an anesthetic agent.

The appropriateness of the chapter on analeptics is well stated in its opening sentence, "It seems appropriate after detailed discussion of the depressant drugs such as the derivatives of barbituric acid, particularly their effect on respiratory function, to consider, at least briefly, the value of respiratory stimulants and analeptics in combating the depressing effects of these drugs."

The final chapter, which discusses intravenous anesthesia for military surgery, is timely, and Dr. Adams was wise in covering this aspect of the subject in a separate and final chapter, thus making for a more general and prolonged usefulness of the book.

The bibliographies after each chapter are extensive.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Allergy in Practice. By Samuel M. Feinberg, M.D., associate professor of medicine and chief of the Division of Allergy, Northwestern University Medical School. With the collaboration of Oren C. Durham, chief botanist, Abbott Laboratories. Chicago: The Year Book Publishers, Incorporated, 1944. $8.00.

This new work on allergy has been written for the benefit of not only allergists but also of practicing physicians. The arrangement of the book is practical, since the clinical parts of the text are set in type of normal size, and controversial and other material are in smaller type. In the work are embodied Dr. Feinberg's investigations on fungi allergy, as well as the thirty years' experience of Dr. Durham on pollens and pollen allergy. In addition to asthma and hay fever, many other allergies, including sensitivity, are adequately discussed. Diagnosis and treatment are especially emphasized.

The Dental Treatment of Maxillo-Facial Injuries: With supplementary material on cases and techniques. By W. Kelsey Fry, M.C., M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.), consulting dental surgeon to the Royal Air Force, consulting dental surgeon to the Ministry of Health, and dental surgeon to Guy's Hospital; P. Rae Shepherd, L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit; Alan C. McLeod, D.D.S. (Penn.), B.Sc. (dent,) (Toronto), L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit; and Gilbert J. Parfitt, M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit. With a foreword by Professor F. R. Fraser, M.D., F.R.C.P., director general, Emergency Medical Service, and a section on fractures of the middle third of the face by A. H. McIndoe, M.S., F.R.C.S., F.A.C.S., consulting plastic surgeon to the Royal Air Force, and surgeon-in-charge, East Grinstead Maxillo-facial Unit. 8°, cloth, 434 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. $6.50.

This is an American edition of an English work published in two parts and comprising lectures and demonstrations given to members of the English armed forces at East Grinstead Maxillo-facial Centre. The purpose of this work is to provide simple instruction in the treatment of injuries of the face as it concerns the dental surgeon.

The Romance of Medicine: The story of the evolution of medicine from occult practices and primitive times. By Benjamin L. Gordon, M.D., attending ophthalmologist, Shore Memorial Hospital, Somers Point, New Jersey, and Atlantic County Hospital for Tuberculosis, Northfield, New Jersey. 8°, cloth, 624 pp., with 145 illustrations. Philadelphia: F. A. Davis Company, 1944. $5.00.

This new work on the history of medicine emphasizes primitive medicine and its relation to the development of modern medicine. The author believes that modern medicine and modern customs are truly an evolutionary development of ancient animistic beliefs, and he has attempted to present a readable but comprehensive account of the ideas alike in the state of health and disease of our savage, semicivilized and civilized ancestors: what their thought was concerning embryology and anatomy, their ideas of the controlling forces governing the human mechanism, their concepts of the mind and soul, and the role it was assumed to play in the human economy.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held at the Peter Bent Brigham Hospital on Tuesday, January 9, at 8:15 p.m.

LAWRENCE CLINIC

The Lawrence Clinic has recently been reorganized. Captain G. F. Clark, U.S.N. (retired) will direct the Clinic, and arrangements have been made with the Executive Committee of the Lawrence General Hospital, composed of Drs. Harold R. Kurth, Rolf C. Norris, John J. Hartigan, Z William Colson, Richard J. Neil and Percy J. Look, whereby the staff of the Lawrence General Hospital will act as the staff of the Lawrence Clinic. When the work of the Clinic increases and more physicians and dentists become available, the program of services will be modified accordingly.

NATIONAL CONFERENCE ON MEDICAL SERVICE

Postwar distribution of medical care will be the theme for the nineteenth annual session of the National Conference on Medical Service to be held in the Red Lacquer Room of the Palmer House, Chicago, on Sunday, February 11, 1945. Medical legislation, physical-fitness programs, the rehabilitation of veterans, the latest word from the Washington front and the relation between labor and farm groups and medicine are among the topics to be discussed by nationally known speakers. Also listed on the program will be an open discussion on prepayment medical plans, the principal advantages and defects of both service and indemnity types of insurance being presented. Congressman Arthur L. Miller, of Nebraska, author of the Miller Bill to unify certain health services, is to be among the speakers. All members of the American Medical Association are invited to attend. Detailed programs of the conference are now ready and may be obtained by writing to Cleon A. Nafe, M.D., secretary, National Conference on Medical Service, 822 Hume Mansur Building, Indianapolis 4, Indiana.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 11

FRIDAY, JANUARY 12

*9:00–10:00 a.m. Cancer of the Pancreas and Ampulla Relative to Diagnosis and Resection. Dr. Richard B. Cattell. Joseph H. Pratt Diagnostic Hospital.

10:50 a.m. Malignant Tumors. Dr. George E. Morris. (Postgraduate clinics in dermatology and syphilis.) Dowling Amphitheater, Boston City Hospital.

SATURDAY, JANUARY 13

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, JANUARY 15

*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

(*Notices continued on page xvii*)

NOTICES (*Continued from page 30*)

TUESDAY, JANUARY 16

*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, JANUARY 17

*9:00-10:00 a.m. Breast Cancer: Problems of diagnosis and treatment. Dr. Joseph Tartakoff Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

JANUARY 9. Harvard Medical Society. **Page 30.**

JANUARY 11. Tropical Diseases (Particularly Malaria) as They Affect New England. Dr. W. C. McCarthy. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 17. New England Society of Physical Medicine. **Page xv,** issue of December 21.

JANUARY 20 and 21. Forum on Allergy. **Page 638, issue of November 2.**

FEBRUARY 3. American Board of Obstetrics and Gynecology. **Page 696,** issue of November 16.

FEBRUARY 11. National Conference on Medical Service. **Page 30.**

FEBRUARY 19. American Board of Internal Medicine. **Page 436, issue** of September 21.

MAY 22-24. Hotel Statler, Boston. Annual meeting of the Massachusetts Medical Society.

SEPTEMBER 17. American Public Health Association. **Page 752, issue** of November 30.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

JANUARY 18. Brockton Hospital, Brockton.
FEBRUARY 15. Jordan Hospital, Plymouth.
MARCH 15. Goddard Hospital, Brockton.
APRIL 26. Toll House, Whitman.
MAY 17. Lakeville Sanatorium, Lakeville.
All meetings will be held at 11 a.m.

WORCESTER

JANUARY 10. St. Vincent Hospital, Worcester.
FEBRUARY 14. Worcester State Hospital.
MARCH 14. Worcester Memorial Hospital.
APRIL 11. Hahnemann Hospital, Worcester.
MAY 9. Annual meeting.

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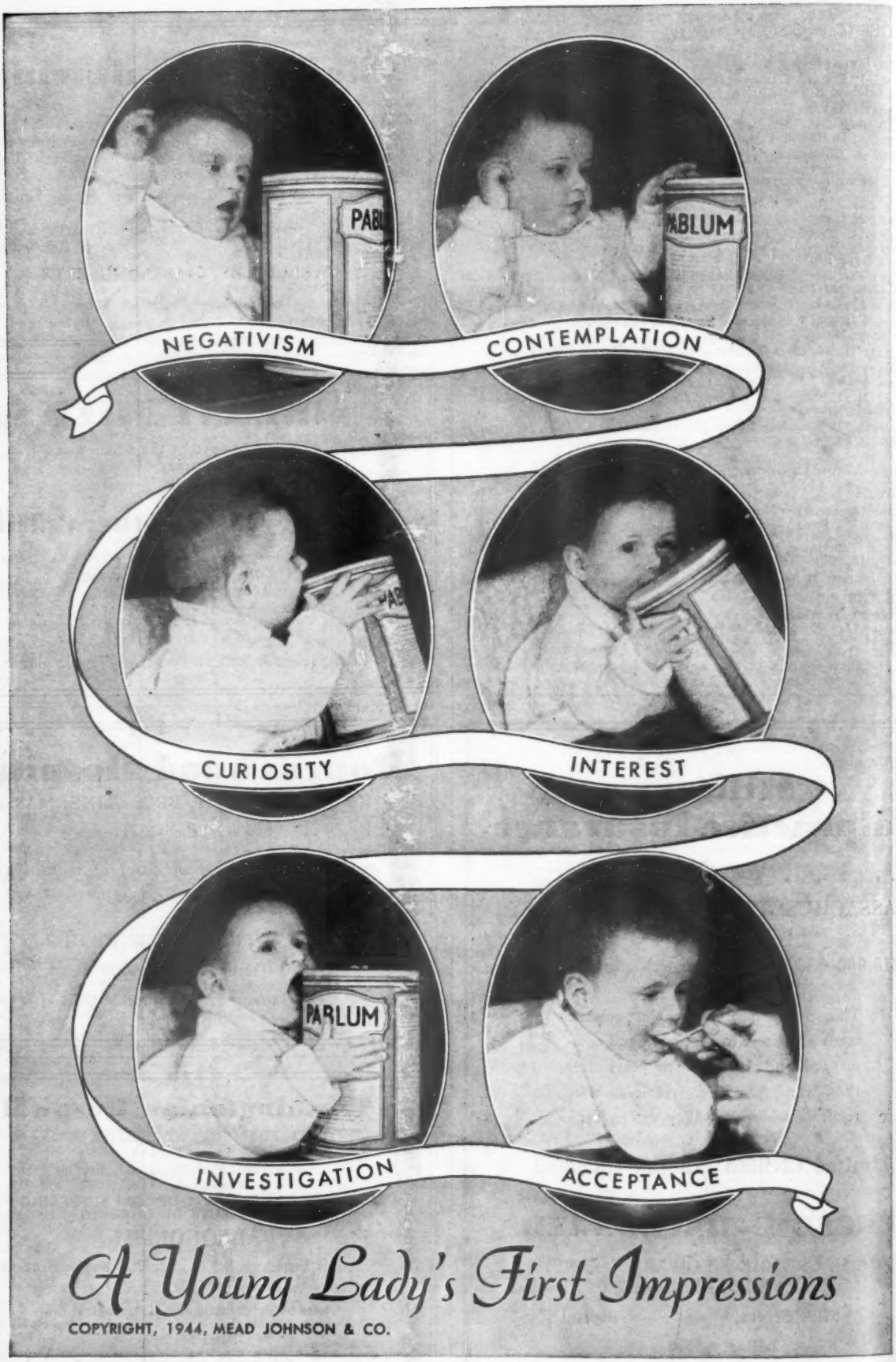
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